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MEDICAL TIMES



Diabetes and Hypertension
Some Preadolescent Fugues
Anomalies of the Thyroid
Prolonging Penicillin Levels
Appendicitis • Lichen Planus
Liver Dysfunction • Miscellany
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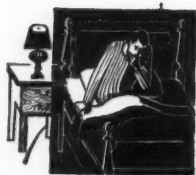
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Vol. 76

September 1948

No. 9

The Journal of the American Medical Profession



*when **night cough**
produces . . . insomnia*

Syrup Sedulon, a new, non-narcotic cough preparation, usually controls "night cough" which robs the patient of needed sleep. Syrup Sedulon, given in therapeutic doses, seems to act specifically on the cough reflex without interfering with heart rate or respiration. Because of its mild sedative effect, the patient sleeps well, and next day experiences no after-effects. Sedulon, the unique active ingredient, has a wide margin of safety, is well tolerated, and remarkably effective even in persistent "night cough."

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Progressiveness and Complications in Diabetes and Hypertension

Frederick M. Allen, M.D.

New York, N. Y.

The widely divergent opinions still publicized concerning these disorders give occasion for a re-statement of views which I have long held and which were voiced at medical meetings, including discussions at the recent A.M.A. Convention.

Diabetes

It is now settled beyond dispute that hydropic degeneration of pancreatic islands represents the anatomic breakdown of an endocrine organ by functional overstrain. This overstrain can be produced by injections of anterior pituitary substance (Young) or by the simple chemical stimulus of repeated glucose injections (Dohan and Lukens), so that permanent diabetes can thus be produced in normal animals. We thus have a clear experimental explanation of the long familiar clinical fact that poorly controlled diabetes with hyperglycemia becomes progressively and irreparably more severe. The once universal belief in a spontaneous progressiveness of diabetes is not now tenable.

It is deceptively easy to keep diabetic patients comfortable with a wide variety of diets with the aid of insulin. There is every gradation of opinion regarding control of the sugar; prevention of hyperglycemia, prevention of glycosuria with disregard of hyperglycemia, permission of slight glycosuria, and total disregard of glycosuria and hyperglycemia. Also even now, twenty-six years after the discovery of insulin, there is a surprising confusion concerning the so-called complications of diabetes. One minority opinion at present is that they are an integral part of the disease and must appear after a long duration, such as twenty years, regardless of treatment. The corollary is that treatment should be conducted with a view to immediate comfort and convenience and with test. Recently I have had a number of my disregard of glycosuria. Any aggravation

of diabetes due to hydropic degeneration can be covered by insulin dosage high enough to maintain weight and freedom from acidosis.

According to the orthodox view which is still held by the majority, the complications are influenced by control of the diabetes. Nevertheless the standards of control are widely variable, as already mentioned. The concrete fact must be faced that the complications of diabetes are very frequent and few cases of more than ten years' standing are free from arteriosclerosis. One result of the introduction of insulin has been a marked increase of complications, especially the arterial ones, because more patients live long enough to acquire them.

Instead of the theories incriminating individual foodstuffs, first sugar, now fat, it is possible to conceive of diabetes simply as a specific malnutrition which lowers resistance and predisposes to deterioration in all organs, including the arteries. Although I have always been opposed to the over-balanced diet fads, I am not convinced that a relative preponderance of fat will cause arteriosclerosis if the diabetes is controlled, or that a preponderance of carbohydrate will protect against arteriosclerosis if the diabetes is uncontrolled. According to this theory, the blood sugar is chiefly important as the most delicate index of control of the diabetes. If the diabetes is kept controlled according to this standard of normal blood sugar, the patient should be able to live out a normal lifetime free from any symptoms or complications of diabetes. This is the promise which I actually give to every patient as his inducement to follow instructions and as his foundation of mental peace and hope.

It is evidently possible to put these discordant theories to a clear-cut decisive patients undergo tests by specialists for a thorough and impartial judgment of their

condition, including especially eyegrounds, electrocardiograms and x-rays of leg arteries. At several recent meetings I have shown lantern slides of some of these patients, ranging in age from 14 to 76 years, with diabetes of 20 or more years' duration in all the older ones. The normal findings in these cases, the normal pregnancies in the women, especially the absence of arterial lesions, are not exceptional. I have a standing challenge to physicians to find any diabetic complications in any of my patients who have followed treatment. There is no lack of such lesions in patients whose diabetes was originally neglected, or who have wandered away to be managed only according to immediate convenience and maintenance of weight without acidosis. Rebellion is limited to those patients who object to regularity and discipline. It is not forced by hardships or incessant insulin reactions, which are unnecessary except in the rare cases of special instability. Also there is no demand for the impossible. Brief hyperglycemia or glycosuria, corrected within a few days, is compensated unless it is too often repeated. My belief is that the so-called "controlled" cases which have organic or arterial degenerations will be found, on scrutiny of their records, to have been through long and repeated periods of markedly abnormal blood sugar. My experience of thirty-odd years convinces me that diabetic complications are uniformly preventable, and if they are already present when treatment is begun their further progress can generally be arrested.

This conclusion, if true, has weighty moral consequences, for it means that every diabetic complication is somebody's fault. The ugly fact that at this long time after the means of thorough control was furnished by insulin, the overwhelming majority of long-standing diabetic cases show arterial lesions with a high incidence of disability and death, is in my opinion chargeable against the large oligarchic institutions, which I have criticized in regard to their clinical policy*, and which

undeniably have failed in their scientific duty to instruct the general profession correctly on this important problem. Physicians at large are willing to learn, but they have been confused by contradictory and predominantly untrue teaching on this matter which could have been settled positively long ago. The important practical lesson is that diabetes should be treated not merely according to immediate comfort but with emphasis upon the condition many years in the future. Physicians who cannot maintain this degree of control should not treat diabetes. It is mainly important to establish the right standard, for if physicians are convinced of it they will generally conform to it. It is also a duty to assure patients that diabetes need not end in blindness, gangrene or death, and that reasonable care can be rewarded by a life of health and efficiency.

Hypertension

Essential hypertension is another disease characterized by progressiveness and complications, chiefly arterial. It likewise involves the responsibility of setting up an individual contention against the teaching of all the great institutions and authorities, with the very serious consequence of discredit for the individual if he is wrong and responsibility of the institutions for a large mortality if they are wrong. Theoretical evidence of the relation of salt to blood pressure, including the positive proofs of the raising of pressure in animal experiments, must be omitted here. My clinical publications in support of salt-free diet, beginning in 1920, included statistics of 180 cases studied during four years, but this principal paper has unfortunately not been available to most practitioners. After more than 20 years of suppression, interest in this diet has lately been awakened and our results have received confirmation, but academic opposition still persists and wields a monopoly of funds for investigation.

Though the above-mentioned publications gave full credit to the prior French suggestions, this work was strictly original in its beginning and also contained the following strictly new features which are

* N. Y. State J. Med. 48: 1306, 1948.

indispensable for successful treatment, the lack of them being sufficient to account for the French failure:

1. The hypothesis of chloridemia, which had been the weak foundation of the French concept, was overthrown by proof that chloride retention is not a necessary concomitant of hypertension or prerequisite for benefit by salt restriction.

2. The necessary standard of strictness was first introduced in my work, and has been adopted by the academic writers after many years of delay. Correspondingly, salt deficiency symptoms were described for the first time, the former diets in France and America having been too lax to create any risk of such symptoms. This was also the first prohibition of sodium bicarbonate and other non-chloride salts.

3. The study excluded psychic, weight, protein and other factors which are still discussed without reference to it. It also set up the classification of responsive and refractory cases which has been adopted by later writers, but it alone was carried far enough to report the benefits in initially refractory cases when the diet was continued for years.

4. Benefits of salt-free diet were described for the first time in: (a) retinitis, (b) puerperal eclampsia, and (c) congestive heart failure, with suggestions for several other conditions.

5. As against the mass of heterogeneous elevations of blood pressure which still make confusion in current discussions, essential hypertension was conceived as a distinct specific disease, which happens to be named from its principal symptom.

6. The experimental and clinical evidence was interpreted in support of the view that saltless diet is capable of specifically arresting progress and preventing complications, so that its efficient application, especially in early stages, offers a rational solution of the problem of hypertensive mortality.

Owing to the opposition, my personal experience is now unique in comprising several thousand cases treated by diet during twenty-eight years. As the results are merely confirmatory of the original statistical study, they may be summarized in

broad statements as follows:

First, early relief of headache, dizziness, dyspnea, palpitation and other symptoms is evident in most cases.

Second, complications involving stasis and edema, such as retinitis and congestive heart failure, often subside dramatically. Anatomic scleroses, such as are represented in angina and claudication, are necessarily less responsive or refractory.

Third, albumin and red cells do not necessarily represent a fixed alteration of renal permeability but often clear up under diet.

Fourth, the main conclusion of the earlier work is sustained by long experience, namely, that benefits obtained with salt-free diet are permanent and tend to increase rather than decrease with time. This is a distinction from all medical or surgical palliations and evidence of the specificity of the treatment.

Fifth, complications are uniformly prevented. Cerebral and cardiac accidents due to preexisting sclerosis are necessarily possible and are in fact a frequent cause of death, delay or reduction of such accidents being the only claim of treatment. But treatment begun at a suitable stage prevents such scleroses and likewise retinitis, uremia, angina and congestive heart failure. This sweeping declaration challenges disproof. If true, it is the final proof of specificity of this treatment.

The necessary permanent cooperation of patients has been obtainable by the symptomatic relief and provision for reasonably appetizing as well as thoroughly accurate diets. Instructions for this purpose were given in my small book (*Treatment of Kidney Diseases and High Blood Pressure*), published in 1925 and still obtainable on order. It is a satisfaction that not one word in regard to the method or its results has had to be changed with time. The direct factual conflict, between the academic clinicians who can observe no benefit from salt restriction and physicians who agree with my observations, is submitted to the free profession for decision. Again the personal risk is justified by the high mortality which is at stake.

1031 FIFTH AVENUE

Lichen Planus

Case History with a Review of the Literature

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Case History

White, male, at 19 typhoid fever which left an ileitis. At 28 excision of 2 tuberculides on finger tips of right hand. At 61 an eruption—macular in shape—on ulnar surface of right forearm (Fig. 1). Instead of healing, this lesion scabbed over and the scab would break off, at approximately monthly intervals, leaving a bleeding surface. It was thought to be tuberculous.

At 63 a similar lesion appeared over the sacrum (Fig. 2). At 64 this lesion was biopsied and pronounced lichen planus ruber. At 71 a similar lesion appeared in the palm of the right hand (Fig. 3). It started near the center and fanned out toward the periphery to form a triangle (see cut). This lesion healed after some months but left a "wart" (glomus) at the base of the thumb and a dimpled surface over the rest of the triangular area.

The constitutional ailments during these years were vasomotor instability, some infiltration at the bases of the lungs (chronic bronchitis), recurrent upper respiratory affections, and mild arthralgias.

The laboratory findings were always within normal limits, although the cholesterol was high (198-250).

Itching seemed to be present only in the periphery of the lesions and only when the scab was about to fall off. (Swelling of the tissues underneath the scabs.) There was also some pain at these times.

Arsenic in the form of Asiatic pills caused only constitutional malaise (nausea, diarrhea, headache, lowered blood pressure) with no apparent effect on the lesion.

Literature

The references to lichen during the 19th

and 20th centuries have not been helpful. The pathogenesis has been marked down as unknown. Only in the last 15 years has the pathology been delineated. And the suggestions for treatment have not been more than would be included under the word, symptomatic.

Here are characteristic excerpts beginning with the more recent:

W. C. Cutting in his *Manual of Therapeutics*, p. 376: "Lichen planus is a chronic disease characterized by tiny papules on the flexor surfaces of the large joints, and at times by oral lesions. The disease is self-limited but tends to recur."

J. F. Burgess, in the *Canadian Medical Association Journal* for Feb. 1941, gives a good description of the classic lesion, thus:—"Clinically the primary lesion is a small violaceous polygonal papule with a plateau-like surface which reflects the rays of light, and not infrequently is covered with fine striae. In general the histologic picture is that of a specific inflammatory eruption with a characteristic band-like infiltration of cells in the upper part of the



Fig. 1. Lesion on forearm some 14 years after its start.

true skin, over which there is a hyperplasia of some elements of epidermis There may be a simple erythematopapular form of the disease, or marked hypertrophic plaques of long duration. Atrophy may also supervene and few of the original primary lesions of the skin are seen."

Sutton in his 10th edition (1939) quotes McCarthy as of 1931: "A generalized hyperkeratosis with circumscribed areas of parakeratosis and widening of the stratum granulosum."

In Ormsby one used to find 25 titles. The attempt was made to reconcile the various classifications, e.g., the lichen ruber of Hebra is the pityriasis rubra of later writers. He would make lichenification a condition due to scratching and therefore preceded by pruritus. The newest edition of Ormsby and Montgomery does something toward clarifying the syndrome.

Kaufman-Reimann (1929): "Lichen is a term reserved for very chronic skin diseases in which nodules are formed which, apart from their growth and desquamation, remain unchanged as such, and eventually undergo involution, never changing into vesicles or pustules."—III, p. 2100.

Riehl and Zumbusch (translated by Ludy, 1925) make lichen simplex a type of eczema; lichen ruber inflammatory and on flexor surfaces. Lichen sclerosus et atrophicus is for them the same as lichen planus.

McFarland, 1904, p. 580, wrote that lichen planus occurs in persons of neurotic temperament, and is due to a disturbance of innervation. Thus Torok found inflammation of the upper layers of the corium with secondary changes in the epidermis. The papillae and the zone underneath are infiltrated with leukocytes, and are edematous. Rete cells proliferate to obliterate the papillae or enlarge them by growth downwards. The corneum (stratum) is thickened. Conic masses of horny epithelial cells form about sweat glands leaving central depressions when exfoliated. The etiology is not understood.

One of the most elaborate attempts at description of the lesion was in German, that of Lesser (*Hautkrankheiten*, Berlin,



Fig. 2. Lesion on back some 8 years after it was noticed. (The upper lesion was the first.)

Vogel, 10th ed., 1900, p.47) of which the following is a translation: "On the normal skin there appear very small, needle-point sized, colorless nodules, which can be seen by the naked eye only by reflection and that by oblique lighting. As these nodules increase in size they become small, slightly raised, round or polygonal, light yellow or reddish papules, which, without scaling, glisten like the original nodules and seem as if made of wax (on account of their slight translucence). While the individual papules grow, at most to the size of a millet seed, they take on a decidedly red color but are never as dark as the papules of lichen ruber acuminatus, but rather show for the most part a more rose-red tint. The papules are not arranged in definite patterns, except in the circular forms here and there, but not generally. On the other hand, regressive changes frequently occur. That is, as soon as the papules have reached the size of a hemp seed, a central depression appears which at first appears as if made by a needle puncture but which increases in size and shows at the base a brown or grayish-brown discoloration. Thus there develops a cockade-like figure with the same type of center and glistening red walls. Finally there appears an involution of this outer wall leaving a pigmentation of the skin in

its place. But in the meantime there have developed on its outer border fresh papules which in turn regress and leave pigmented areas. Thus the eruption advances until areas the sizes of a quarter to a dollar appear with darker central parts and narrow edges which are built of coalesced lichen papules. The outline of these eruptions, since they are made up of separate papules, is notched and tooth-like. In some cases the papules show no inclination to central regression, but instead form more or less irregular infiltrated patches, which exhibit the above mentioned Russia leather appearance and are surrounded by a swarm of minute glistening macules."

The approach to the literature by way of the texts on pathology did little to clear up the nature of lichen—in spite of the use of the word "lichenification." This discussion really amounted to the dictionary definition, namely, "The conversion of an eruption, such as eczema, into a form resembling lichen." — (Dorland). This would neither support nor refute the charge that lichenification is brought on by scratching an itching skin.

Apparently there must be more to it than local trauma. Is that something vascular failure or deficiency? Or is it "trophic" (In the sense of the word used by the older internists)? The dermatologists have not yet given their answer. As long as the pathogenesis is so obscure, the diagnosis and classification of this large group of skin lesions will remain in doubt.

As to constitutional causes, such as the lack of vitamins and hormones, the current periodical literature of course offers samples of the usual enthusiasm for new things. But turning to our textbooks, I found this:

Teichmann in Yater's *Fundamentals of Internal Medicine* says (p. 928) that there are no skin diseases definitely attributable to endocrine dysfunction. He also says that there are no skin diseases known in which diet is definitely recognized as the causative factor.

But in a brochure of the Schering Corporation, this statement appears (p.62): "[The male sex hormone] influences the

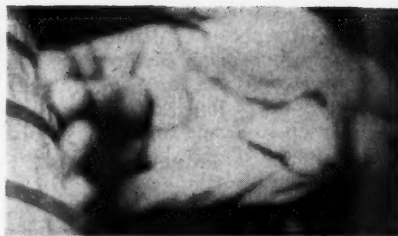


Fig. 3 Palmar lesion just before it broke down, to leave a "wart" (glomus) on the thumb side.

blood supply and pigmentation of the entire human skin and has a beneficial effect in certain skin diseases occurring in late middle life . . . characterized by dryness, fissuring, itching, and eczema." If this is the consensus of opinion among the endocrinologists, then lichen should be suspect. And certainly some specialists in skin diseases do seem to trace a connection between foods and skin lesions.

When it comes to treatment some of the authors are frank enough to admit that there is none. So it comes down to palliative treatment for the pruritus. However, since the development of the vitamins, the administration of both A and B has been urged—apparently on the hypothesis that the lesion is a nutritional one.

Even on palliative treatment there seems to be a healthy difference of opinion. First, those who have a lurking suspicion that there is an exogenous or infectious cause use the salicylate salves. Next, the traditional use of mercury and arsenic is mentioned—although Sutton thinks that mercury may do harm. Third, the group who think of the nutritional aspect as primary advocate lanolin and massage.

Comment

If we are to keep lichen from being a term used to include a number of unknown lesions—from being a catch-all—we must think out the pathogenesis. Since it does not appear to be an infectious lesion we must base our treatment on our belief as

—Concluded on page 399

The Most Recent Advances in Prolonging Penicillin Blood Levels

This summarization attempts to cover all of the known therapeutic information on the subject and is designed as a time-saving refresher for the busy practitioner.

Reprints available.*

The dramatic antibacterial action of penicillin prompted a thorough investigation for its best dosage form. The method of administration governs the rapidity and degree of absorption of the drug. At first penicillin was administered in the form of an aqueous solution (saline or glucose) by intravenous injection. This route provided immediate therapeutic blood levels but the rapid excretion of the penicillin did not allow for maintenance of such levels so that it was necessary to administer the drug every 2 or 3 hours unless the continuous intravenous drip method was employed.

Method of Administration

This unsatisfactory method of administration inspired many workers to seek other means. It was found that penicillin was rapidly absorbed from the muscles but here again the investigators were faced with the problem of maintaining the therapeutic levels.¹ Subcutaneous injections not only caused more pain and discomfort but the absorption by this route was slower and less definite. Even more variable but to a much lesser degree was the absorption following intrapleural, intrathecal, intra-abdominal and intra-articular injections.

Investigation revealed that the desirable level of penicillin in the serum should be maintained at 0.02 to 2.0 units per cc. of serum for the necessary period of time in order to bring about satisfactory results. This level is of course influenced by the

nature and severity of the infection, and the following factors connected with the patient: weight, degree of fluid intake, kidney excretory capacity and others.²

Intermittent Intravenous Injection

Intermittent intravenous injection of 5000 to 40,000 units of penicillin results in effective serum levels immediately but in half an hour there is an abrupt fall so that 20,000 or more units are necessary to provide therapeutic levels for one to two hours.³ This necessitated giving the drug every two hours at least and results in too many venipunctures daily so that the search continued. By means of the continuous intravenous injection of 200,000 to 10,000,000 units daily it was possible to maintain therapeutic serum levels of 0.20 to 9.2 units per cc.⁴ but this method required constant supervision and sometimes resulted in thrombophlebitis from the large amount of fluid injected.

Intermittent Intramuscular Injection

Although the absorption was slower when penicillin in aqueous or glucose solution was administered by intermittent intramuscular injection excretion of the drug was also slower, resulting in the maintenance of therapeutic blood levels for 30 to 45 minutes. It was found that the injection of 15,000 units by this route resulted in penicillin being present in the blood for 2 to 3 hours; for 3 hours with 20,000 units; 4 hours with 35,000 units; 4 to 5 hours with 50,000 units; and 5 to 6 hours with 100,000 units.⁵ It was possible to maintain sufficient concentration in the blood for 12 hours with 6 doses

* From the Editorial Research Department of the MEDICAL TIMES, 67 Wall Street, New York 5, N. Y.

of 15,000 units each every 2 hours. By this means an effective concentration was maintained for a longer period with a total of 90,000 units whereas with 100,000 units given at one time the level lasted for approximately half the time. In infants and children the level in the blood was highest within one-half hour after administration. This level was still fairly high at the end of an hour but dropped rapidly during the second hour. However, low concentrations were observed for 3 or 4 hours.⁶

Continuous Intramuscular Injection

Continuous intramuscular injection of penicillin resulted in serum levels similar to those obtained by means of continuous intravenous drip. With dosages of 100,000 to 3,000,000 units the levels varied from 0.1 to 3.0 units per cc. The administration of 500,000 units daily resulted in levels of 0.35 units per cc.; 1,000,000 units, 0.6 units; 2,000,000 units, 1.5 units; 3,000,000 units, 2.0 units; and 5,000,000, 5.0 units.

Various methods have been tried in this search for a way of maintaining the therapeutic serum levels of penicillin. The two approaches to the problem involved either delaying its absorption or its excretion.

One group recommended that the site of the intramuscular injection be chilled with ice for 1 to 2 hours before and 5 to 12 hours after each administration. By this means it was found that therapeutic serum levels were maintained for 6 to 12 hours after administration of 50,000 and 100,000 units in a single injection.^{7,8}

Romansky Formula

In 1944 Romansky and Rittman proposed the formula for what is now known as penicillin injection in oil and wax.⁹⁻¹¹ This is a suspension of penicillin calcium or crystalline penicillin G sodium in a menstruum of peanut oil or sesame oil in which approximately 4.8 per cent (w/v) of white wax is dispersed. The wax serves to enhance the delayed absorption brought about by the fixed oils. This formula has been employed extensively and has been found to maintain satisfactory serum levels

(0.03 units per c.c.) of penicillin for 12 to 24 hours. This concentration of 0.03 units per cc. of blood is considered to be well above the *in vitro* inhibitory concentration necessary for most penicillin-sensitive organisms. The time varies of course with the dose. The absorption and excretion following intramuscular injection is variable, probably due to the location of the injection, for it is best absorbed from the muscles and is slowly and irregularly absorbed from the fascial spaces. More uniform and slower absorption occurs from the subcutaneous tissues.²

In order to maintain the minimum assayable levels in the serum it is necessary that 2500 units of penicillin be absorbed every hour.¹² In order to produce this state it is believed that 300,000 units of penicillin in oil and wax must be given intramuscularly every 12 hours. Single daily doses are not considered sufficient unless 600,000 units are given, particularly by subcutaneous injection, but this is an expensive procedure and not always of definite value.

Unfortunately the beeswax in the Romansky formula possesses certain disadvantages. Pain is produced at the site of the injection and a number of cases of indurations and even sterile abscesses have been observed to occur some time after the injection.

This product is available from several manufacturers in vials for use in clinic, hospital or office; in cartridges for use in disposable or permanent syringes (cartridges are double-celled, providing the single dose of 300,000 units in one cell and a sterile aspirating test solution in the other to guard against accidental intravenous injection); and in disposable syringe units.

Cleansing of Syringes

In those instances where permanent syringes are used it is important that a certain procedure be followed in cleaning and sterilizing such syringes. They may be sterilized by autoclaving, ordinary boiling or immersion in 70 per cent alcohol. In order to insure removal of all remaining traces of moisture which may be left in syringe and needle, both should be rinsed in ether and air pumped through after ex-

pling the ether so as to evaporate all remaining traces of ether.

It is necessary to employ careful technic at this point so that the syringe does not become contaminated by hands or other equipment while it is being dried. Carbon tetrachloride, chloroform, acetone, benzene, toluene or carbon disulfide should be used to clean syringes which have been used to administer penicillin in oil and wax. Any residual traces remaining after use of one of the solvents may be removed with warm water and soap. Carbon tetrachloride provides the most rapid cleansing. All traces of solvent must be removed by thoroughly rinsing in alcohol or water.

Retarding Substances

Other substances have also been used for their ability to retard the absorption of penicillin. Some of the combinations used include: (a) 50,000 units of penicillin in 5 cc. of 20 per cent solution of ossein gelatin with 0.025 per cent solution of phenylephrine hydrochloride;¹³ (b) aqueous solutions with varying amounts of epinephrine;¹⁴ (c) crystalline penicillin combined with human plasma protein to form a large penicillin protein complex;¹⁵ (d) pectin;¹⁶ (f) lanolin-like substances. Epinephrine and neo-synephrine were employed for their vasoconstrictor properties. One product available on the market consists of a suspension of crystalline potassium penicillin G (benzyl penicillin) 300,000 units per cc. with 0.3 mg./cc. of epinephrine in peanut oil. Satisfactory therapeutic blood levels have been claimed for a period of 12 hours following a single injection of this product. The oil not only retards absorption but also serves to prolong the vasoconstrictor action of the epinephrine, thus prolonging in turn the vasoconstriction of the blood vessels surrounding the injection area, resulting in retarded absorption of the penicillin. When this product is used the ampul must be shaken for 30 seconds in order to insure uniform suspension of the solid particles. A sterile, dry, 19 to 21 gauge needle with a sterile, dry syringe is employed. To facilitate withdrawal of material it is wise to inject 1 to 2 cc. of air into the vial.

Also found suitable for intramuscular injection were emulsions prepared from aqueous solutions of penicillin, peanut oil and a lanolin-like substance. A similar vehicle was prepared from oxysterins and cholesterol esters prepared by a special process and dispersed in highly refined peanut oil. Both of these vehicles were found of value in treating gonorrhea and the latter in syphilis.^{17,2}

Inhibition of Penicillin Excretion

Another method by which the action of penicillin may be prolonged is the inhibition of penicillin excretion. Penicillin circulates through the renal blood system and 80 per cent of it is eliminated by the renal tubules and 20 per cent by the glomeruli. It was thought that suppression of excretion from the renal tubules therefore would prolong the effect of approximately 80 per cent of the penicillin. Several substances were tested for this purpose. Pitressin was used to decrease the blood flow through the kidney but this did not appear to be the ideal method. Iodopyrin¹⁸ (Diodrast, N. N. R.) was tried as were para-amino-hippuric acid,^{19,20} benzoic acid and sodium benzoate.^{21,22} Both iodopyrin and para-amino-hippuric acid were found to successfully suppress the excretion of penicillin and with sufficiently high doses the suppression was complete. They are excreted by the same mechanism and as rapidly as is penicillin and therefore compete for the same tubular excretion with the penicillin and saturate the transport mechanism so that penicillin elimination is inhibited. Para-amino-hippuric acid²³⁻²⁵ could be given in large dosages with no toxicity but it was not absorbed on oral administration. However, in both instances it was necessary to administer intravenously such large quantities that it was not practical. The use of para-amino-hippuric acid was successful in maintaining high plasma concentrations of penicillin in diseases where such high levels were absolutely necessary.²⁶⁻²⁸

From these studies it developed that a satisfactory compound should not be excreted like penicillin by the tubules but should be limited to excretion by glomerular filtration. Furthermore glomerular fil-

tration could not be suppressed due to the fact that such action would interfere with filtration of all crystalloids. The agent needed to be one having an affinity for the transport mechanism but not inhibiting other tubular mechanisms such as glucose, arginine or urea reabsorption, or renal excretion of sulfonamides.

Caronamide

After investigation of various compounds 4'-carboxyphenylmethanesulfonamide was found to produce the desired reversible inhibition of tubular excretion of penicillin. This compound was given the name Caronamide.

Penicillin is normally transferred from the capillaries through the tubular epithelium by means of a cellular enzymatic function. The epithelial cells excrete the drug into the lumen of the renal tubule which proceeds to eliminate it rather than reabsorb it as it does glucose and other substances. Caronamide, which is excreted solely by glomerular filtration, competes with the penicillin for this enzyme responsible for tubular excretion of penicillin. Thus the penicillin has no means of transport from the blood stream to the lumen of the renal tubule and the high and prolonged plasma concentration is maintained.^{29,30}

The effect of Caronamide lasts for about four hours dependent to a great extent on the optimal concentration in the blood stream. As the compound is eliminated by glomerular filtration the enzyme is again released unchanged and penicillin excretion resumes its normal pattern: Caronamide only maintains the blood level of penicillin and it is not synergistic insofar as antibacterial action is concerned. Tests of Caronamide for possible effect on bacteriostatic activity of sulfonamides in cases where both penicillin and sulfonamide must be given revealed no significant effects.

Penicillin in 100,000 unit dosage with Caronamide produced higher plasma concentrations than 300,000 units alone. In bacterial endocarditis, a condition which requires extremely high concentrations of penicillin in the blood, Caronamide in

doses of 1.5 to 3.0 Gm. every 3 hours for 10 to 28 days caused higher levels than penicillin alone could ever produce.

Administration

Caronamide can be administered orally with penicillin given by any route. The dose recommended is 1.5 Gm. to 3.0 Gm. every 3 hours or 2.0 to 4.0 Gm. every 4 hours with penicillin. Patients under 60 years of age may require 3.0 Gm. every 3 hours or 4.0 Gm. every 4 hours. Patients with impaired renal function or those over 60 years of age require only 1.5 Gm. every 3 hours or 2.0 Gm. every 4 hours. Children weighing 84 lbs. (40 Kg.) or less should be given 0.2 to 0.4 Gm. per Kg. of body weight daily. This dose should be administered in equally divided doses every 3 or 4 hours.

Caronamide administration in conjunction with penicillin lessens the cost of penicillin therapy because the usual dosage of penicillin can be given and a greatly enhanced effect achieved; the time interval of 2 to 3 hours between doses can be lengthened to 4 to 6 hours by the intramuscular route; or the dose may be reduced to one-half or one-quarter and the time interval remain the same.

Penicillin is usually orally administered in doses of 100,000 units every 3 hours or 800,000 units daily. Of this only 20 per cent or 160,000 units is absorbed into the blood stream. Administration of Caronamide with one-fourth the dosage of penicillin or 200,000 units allows for absorption of 20 per cent or 40,000 units but since Caronamide increases by 4 times the plasma concentration of penicillin this is equivalent to 160,000 units, the same level achieved by giving 800,000 units of penicillin alone. Caronamide has been shown to be of particular value in enhancing the effect of penicillin in the therapy of gonorrhea. With it only one dose of penicillin has been necessary in 34 of 36 patients in one study.³¹ Caronamide has also shown some enhancement effect on plasma concentrations of penicillin administered in peanut oil and beeswax as well. Phenol red and hippuran also have been tried.

Insoluble Salts

The development of relatively insoluble penicillin salts such as aluminum penicillin and procaine penicillin is another approach to the problem of finding an ideal method of prolonging penicillin blood levels.

Aluminum penicillin is a poorly soluble penicillin salt which has been found to give therapeutically effective blood levels for at least 12 hours following injection of 300,000 units suspended in peanut oil. It is also administered orally accompanied by sodium benzoate, which is believed to inhibit the destruction of penicillin by penicillinase in the intestinal tract.

Procaine Penicillin

One of the greatest advances in the work with penicillin has been the development of procaine penicillin, which has already supplanted, to a considerable degree, penicillin in oil and wax. Procaine penicillin is only sparingly soluble in water in contrast to the high degree of solubility of the sodium, potassium and calcium penicillins and is also rather poorly soluble in oils. This insolubility is an asset for as a result procaine penicillin is more slowly absorbed and therapeutically effective blood levels are maintained for a longer period of time. The administration of this salt in sesame or some similar oil also aids in retarding

absorption and excretion. When suspended in oil it was found that at least 50.0 per cent of the total weight of the particles are 50 μ or more in length.³² The size of the particle has been shown to be of importance in slowing the absorption of penicillin.^{33, 34} Early reports showed that absorption of soluble penicillin salts was delayed when the particle size exceeded 50 μ in length but recent investigations of procaine penicillin with aluminum monostearate have shown that a substantial decrease in the particle size greatly retards absorption and prolongs blood levels.^{34a} However, this subject is still controversial at this time.

The elimination of the wax not only provides a fluid preparation at room temperature but it also should reduce the incidence of local reactions (lumps, etc.) which occurred when the oil and wax product was administered since these were believed to be due to the wax. Some have stated that the presence of the procaine provides a local anesthetic action which reduces the incidence of pain at the site of injection.

Clinical Trials

Clinical evidence has shown that therapeutic blood levels for 24 hours are produced by a single injection of 300,000 units in 95 per cent of patients³⁵ whereas

TABLE 1
BLOOD LEVELS OF PROCAINE PENICILLIN IN COTTONSEED OIL*

Patient	Amount administered (cc.)†	1 hr.	2 hrs.	Blood levels (units per cc.)			36 hrs.	48 hrs.
				12 hrs.	18 hrs.	24 hrs.		
1	1		0.496		0.124	0.248		
2	1	0.248		0.124	0.124	0.124		
3	1	0.992		0.248	0.124	0.124		
4	1	0.496		0.248	0.124	0.124		
5	1		0.124	0.124	0.124	0.124		
6	1		0.124	0.124	0.062	0.062		
7	1	1.984		0.124	0.062	0.062		
8	1	0.248		0.124	0.062	0.062		
9	1	0.062		0.062	0.062	0.062		
10	1	0.496		0.124	0.062	0.062		
11	1	0.248		0.496	0.248	0.124		
12	1	0.496		0.248	0.031	0		
13	1	0.062		0.124	0.124	0.062		
14	1	0.992		Not drawn	0.124	0.124		
15	1	0.496		0.248	0.124	0.062		
16	1	1.984		3.968	0.496	0.124		
17	1	0.824		0.824	0.659	0.329		
18	2	0.124		0.124	0.124	0.124		
19	2	1.984		0.496	0.496	0.062		
20	3	0.992		0.248	0.248	0.248	0.031	0
21	4	0.496		0.496	0.496	0.496	0.248	0.124

* Control blood level determinations on all patients were 0.

† 1 cc. contains 300,000 units.

this figure was only 90 per cent when patients were treated with the Romansky formula. A comparison of average blood levels for the two showed 0.312 and 0.039 units per cc. in 12 and 24 hours respectively for the Romansky formula and 0.451 and 0.134 units per cc. for the procaine penicillin in oil. The latter therefore produces blood levels over 3 times those produced by the Romansky formula.

The new drug prepared in a cottonseed oil suspension was administered to 21 hospitalized patients, and the level of the drug in the blood determined. Only one out of the twenty-one showed a blood level lower than 0.062 units per cc. at the 24th hour. Many showed levels of as high as 0.124 units per cc. In one instance the patient was given 900,000 units (3 cc.) and revealed a therapeutic level at the end of the 36th hour. Another case, given 1,200,000 (4 cc.), showed a blood level of 0.124 units per cc. at the end of the 48th hour. No local or systemic reactions were observed.³² (See Table I).

Vehicles

Procaine penicillin has been made available in various types of vehicles. One group has suspended it in refined sesame or peanut oil with or without the aid of dispersing agents and supply it in quantities of 300,000 units per cc. in 1 cc. ampuls, disposable syringes and in 5 and 10 cc. multiple dose vials. Some of the oil suspensions of procaine penicillin are further modified by inclusion of 2 per cent aluminum monostearate or aluminum stearate. This, being a water-repellent substance, still further reduces the rate of absorption of penicillin from the tissues. The addition of this compound in some instances was found to confer upon the finished product the properties of a thixotropic gel. This is defined as a reversible gel-sol phenomenon in which a semi-rigid gel while at rest is converted into a fluid by shaking. At first this property was considered of value but it is now disregarded for it has been found that its development is not important in the prolongation of absorption of procaine penicillin. One product containing 2 per cent aluminum monostearate has been found to

maintain therapeutic blood levels of penicillin for 96 hours following a single injection of 300,000 units. Others are now being tested. Procaine penicillin in oil is stable at room temperature for at least a year and need not be stored at refrigeration temperatures. If it is quite cold it may have to be warmed in order to make it fluid. The oil suspension products without aluminum monostearate should be thoroughly agitated before use due to the separation of the procaine penicillin from the oil.

The syringe must be sterile and dry. Air (1 cc.) should be injected into the vial in order to facilitate the withdrawal of the material. This is done by means of a sterile 18-gauge needle attached to the syringe and inserted through the rubber cap which is rendered aseptic by application of a suitable antiseptic. The material is then withdrawn and a 20-gauge 1½ inch needle used for the injection is attached in place of the 18-gauge one. The injection is given intramuscularly, never intravenously or subcutaneously, because of the danger of formation of an oil embolus as is the case with all oil injections. It should be injected into the upper outer quadrant of the buttocks, but because of its fluidity and anesthetic properties may be injected into the anterior thigh muscles, the triceps or into the deltoid. The drug should not be injected until slight negative pressure on the syringe shows that the needle has not been inserted into a blood vessel. After injection a small amount of air should be drawn through the needle to clear the needle lumen of the procaine penicillin in oil. Pressure should be maintained briefly to control leakage but the site should not be massaged.

If permanent syringes are used they should be cleansed with an aqueous solution of one of the wetting agents such as sodium lauryl sulfate and then rinsed with water. Organic solvents are not satisfactory because they precipitate procaine penicillin. Locked syringes should be soaked in 50 per cent glycerin. After sterilization the syringes may be dried with ether. The disposable type of syringe eliminates all of this difficulty.

Recent announcement was made of the availability of procaine penicillin for administration in aqueous suspension. This product possesses the following advantages: (a) it contains no oil thus avoiding any danger of oil embolism and oil sensitivity; (b) there is no pain at the site of injection and no danger of tissue damage; (c) it is supplied in dry form and remains stable for 12 months; (d) in aqueous solution it retains its potency for 21 days at room temperature; (e) the needle and syringe do not have to be dry in order to inject it; (f) a single injection of 1 cc. (300,000 units) maintains effective blood levels for 24 hours in nearly all cases.

This product is administered in Water for Injection U.S.P. or Sterile Normal Saline Solution, U.S.P. Even dispersion of the product in aqueous suspension is accomplished by means of a hydrophilic colloid which acts as an innocuous suspending agent. The suspension is prepared by injecting the necessary quantity of aqueous vehicle into the vial of procaine penicillin. The vial should be shaken well before withdrawing each dose and only one dose withdrawn into the syringe at one time. The injection should be made within a few minutes so that the full dose of procaine penicillin G is administered. If the suspension is allowed to settle in the syringe, retraction of the syringe piston to make an air space and tilting back and forth of the syringe will resuspend the drug.

Reactions

The procaine salt of penicillin has shown no evidence of tissue irritation or local discomfort from its injection. Negative results have also been reported in systemic toxicity studies.^{35, 36}

Toxicity studies in mice have shown that crystalline procaine penicillin G in peanut oil is approximately one-twentieth that of the toxicity of procaine. The possibility of toxic effects from procaine is rather remote because of the delayed absorption into the circulation so that it is not likely that the concentration could reach toxic levels. Preliminary studies have shown procaine penicillin to have no

more toxicity than its component parts.³⁷ It must be kept in mind, however, that some individuals are hypersensitive to procaine so that if there is any suspicion of an allergy to procaine an intradermal injection of 0.1 cc. of a 1 or 2 per cent solution of procaine hydrochloride should be given preceding procaine penicillin therapy. A positive reaction precludes the use of procaine penicillin.

Mild procaine reactions may be prevented in some patients by administering a quick acting barbiturate. The patient may have an allergic reaction to the penicillin (expected in up to 5 per cent of patients given penicillin) which is evidenced by such symptoms as urticaria, pruritus, angioneurotic edema, erythema, dryness of skin and dermatophytid reactions. In most cases such reactions can be controlled by the administration of one of the antihistaminics concurrently with the penicillin. For adults 50 to 100 mg. orally, 3 times daily, of the former should be sufficient. If the response to the antihistaminic is minimal in 12 hours' time the dose should be increased to 50 to 100 mg. every 4 hours day and night.

If dermatophytids develop the therapy can usually be continued but the patient should be made comfortable by the application of wet soaks or compresses to the areas affected. Penicillin therapy may have to be discontinued for a few days or permanently if the reactions persist and grow worse.

Reactions may also develop after a course of penicillin therapy has been completed. In such instances the condition should be treated symptomatically. Oral magnesium sulfate, calcium and ephedrine, intravenous procaine or an antihistaminic may be indicated. Salicylates are of value if the symptoms are arthritic. Bed rest is necessary in cases of the serum-sickness type of reaction.³⁸

There may be local reactions occurring at the site of injection several days after administration. Relief can be obtained by use of cold compresses. In any case where reactions develop therapy with penicillin should be continued if the severity of the infection warrants. In extreme cases it may

be necessary to suspend penicillin therapy and try some other means such as streptomycin or one of the sulfonamides.

Synergists

In those cases where it may be necessary to administer both penicillin and a sulfonamide there arises the possibility of an altering of the effectiveness of the latter as a result of the breakdown of procaine into para-aminobenzoic acid (paba). This is not believed to be of any significance because of the slow release of the procaine molecule from the site of injection. The concentration of procaine (124.5 mg. in 1 dose) present would result in only 72.3 mg. of paba and at the rate of 1 unit of penicillin per cc. of blood there would be only 0.00024 mg. per cc. of paba.

Toxicity Studies of Vehicles

Toxicity studies of aluminum monostearate have shown it to possess no irritating or toxic properties. This was expected due to the fact that it is so extremely insoluble and its wide employment as an ingredient of ointment bases used for third degree burns in World War II.^{36,39} No sensitivity to sesame oil has been reported thus far.⁴⁰

Indications

Procaine penicillin is indicated in the therapy of:

1. Most staphylococcal infections, with or without bacteremia.
2. All cases of clostridia infections.
4. All anaerobic streptococcal infections.
5. All pneumococcal infections.
6. All gonococcal infections.
7. All cases of anthrax.
8. All cases of pulmonary suppuration with contemplated surgical treatment.
9. All sulfonamide resistant meningococcal infections.
10. Most cases of bacterial endocarditis due to penicillin-sensitive organisms.
11. Swine erysipelas (erysipeloid).
12. Vincent's infection.

13. Prophylactic use following tonsillectomy and tooth extraction in cases of rheumatic fever, congenital heart disease, etc.
14. Syphilis.
15. Actinomycosis.
16. Diphtheria (along with antitoxin).

Dosage

The usual dosage of procaine penicillin is 1 cc. or 300,000 units but because of its nonirritating nature as much as 2 cc. may be given twice a day for 5 to 10 days if necessary. The therapeutic blood level is considered by some to be 0.04 unit.

Gonorrhea—Practically all cases of acute, uncomplicated gonorrhea can be cured by a single intramuscular injection of 300,000 units. In refractory cases a second or more injections of 300,000 units may be necessary. In cases of complications such as prostatitis and epididymitis 4 to 6 intramuscular injections of 300,000 units each are indicated. In gonorrheal arthritis 300,000—600,000 units should be administered daily for a period of 8 to 10 days. In those patients suspected of also having syphilis penicillin should not be administered until the possibility of the dual infection has been eliminated.

Syphilis—Use of procaine penicillin in the therapy of syphilis is still under investigation so that it is impossible to present information on the optimum dosage. However, it can be assumed that the dosage schedule will be essentially the same as for penicillin in oil and beeswax. The committee on Medical Research, the United States Public Health Service and the Food and Drug Administration in a joint statement recommended a minimum dosage of 600,000 units (2 cc.) of penicillin in oil and wax daily for 8 to 15 days, depending upon the stage of the infection. For early syphilis a minimum total dose of 4.8 to 6.0 million units of this preparation is advised. In cases of serologic and clinical relapse of early syphilis, the course of penicillin therapy should be repeated. In conjunction with penicillin, oxophenarsine hydrochloride should be administered two to three times weekly

in six individual intravenous injections of 60 mg. each. In addition, the patient should receive 1200 mg. of bismuth subsalicylate given twice weekly in six individual intramuscular injections of 0.2 Gm. each. In the case of a second relapse of early syphilis after previous penicillin treatment, the use of penicillin should be discarded and chemotherapy with arsenic and bismuth instituted. Because experience in the therapy of syphilis with penicillin is limited it is probable that the true evaluation of this therapy will not be established for some years. For this reason clinical and serologic examinations at least once a month for the first six months and every six months thereafter for at least two to three years should be made in all cases of penicillin-treated syphilis. If a rising titer is obtained or a recurrence is observed, it is advisable to retreat the patient either with penicillin alone in larger dosage or over a more prolonged period of time, or with concurrent administration of arsenic and bismuth. A relapse rate of 25 to 30 per cent may be expected following penicillin therapy. If this rate is believed to be due to relapse, a second course of penicillin with or without arsenic and bismuth therapy may be given. If due to reinfection, a second course of penicillin therapy alone may be relied on, in a total dose of at least 1.2 million units given over a period of one week. Revision of these tentative suggestions will be made as further information is accumulated.

As a result of evidence presented at a recent conference of the Syphilis Study Section of the National Institute of Health it was believed that a one injection treatment for early syphilis with procaine penicillin in oil with aluminum monostearate was on its way to being a fact. About 12 patients have been given a dosage of 1,200,000 to 1,500,000 units in one site at one time which was found to maintain penicillin blood levels for at least 7 days. At that time it was agreed that clinical studies of penicillin in oil and beeswax should be discontinued because the development of newer dosage forms eliminated the possibility of any further gains in the work with this form in the

therapy of syphilis. Procaine penicillin in oil with aluminum monostearate is believed to give longer therapeutic blood levels than procaine penicillin in oil or in aqueous suspension. The studies to be conducted will involve 3 dosage schedules. In the first 1,200,000 units will be given in one injection at one site; in the second the same dosage will be given twice with a period of one week between each injection; and in the third schedule the same dosage will be given weekly for 4 consecutive weeks.

Pneumonia and Other Acute Infections caused by Pneumococci, Staphylococci and Streptococci—In these conditions the minimum dose of procaine penicillin is 300,000 units intramuscularly each day until at least 48 hours after the temperature has returned to normal and evidence of infection has disappeared. If the infection is overwhelming 600,000 units twice a day may be necessary (12 hour intervals).

Meningitis—In meningococcal, staphylococcal, pneumococcal and streptococcal meningitis procaine penicillin is given in dosage of 300,000 units twice a day as a supplement to sulfadiazine therapy. In addition aqueous penicillin (not the forms of procaine penicillin for aqueous vehicles) should be given intrathecally, once or twice daily, in doses of 10,000 to 20,000 units in 10 to 20 cc. of sterile normal saline solution.

Miscellaneous—In other coccal infections such as streptococcal pharyngitis, tonsillitis, erysipelas, cellulitis or mastitis, staphylococcal furunculosis and similar lesions, acute sinusitis and streptococcus carriers the dosage is 300,000 units intramuscularly each day. Procaine penicillin is administered in 300,000 to 600,000 units daily in the treatment of Vincent's infection, erysipeloid (swine erysipelas), and in the treatment of secondary infections. Procaine penicillin is also indicated in the treatment of spirochetal disease, actinomycosis, subacute bacterial endocarditis, infections due to *Bacillus anthracis* and, in conjunction with specific antiserum, in infections due to the Clostridia group of organisms. It is necessary that adequate blood levels be maintained. In conjunc-

tion with specific antitoxin therapy procaine penicillin is used to eliminate the infection and control the carrier state in diphtheria.

Procaine penicillin is of value as a prophylactic agent in tonsillectomy or tooth extraction where there is a history of rheumatic heart disease. Preoperatively 300,000 units are given, which dosage is repeated daily for 3 days.

Dosage in Children

Although more evidence is being accumulated concerning the optimum dosage of procaine penicillin, as high as 100,000 units daily have been given to infants without any untoward reactions. A satisfactory dosage schedule of 0.2 cc. for infants; 0.5 cc. for children up to 10 years of age; and 1 cc. for those over 10 years has been advised by some. In some cases it may be necessary to use penicillin in aqueous solution by intramuscular injection or by some other route where the conditions warrant it.

Advantages of Procaine Penicillin

It is possible to obtain higher blood levels in at least 95 percent of patients when procaine penicillin is employed as compared with other repository forms. As a result the patient's response to therapy is quicker. The decrease in discomfort and the availability of adequate treatment in

the physician's office or patient's home (without hospitalization) make the patient more cooperative, resulting in more satisfactory control. Use of only one daily injection eliminates the need for disturbing sleep as is necessary with earlier forms. There is less possibility of side-effects at the site of injection; and more possible sites of injection are available because of the increased fluidity and comfort. With procaine penicillin fewer total units are necessary than with the aqueous solution of penicillin, which makes for increased efficiency and less expense in treating chronic diseases or prolonged acute diseases. The physical state of the product makes it easy to withdraw without the necessity of warming and if the needle and syringe are dry there should be no clogging. No special solvents are needed for cleaning. Use of the aqueous suspension does not require a dry needle and syringe. Refrigeration of procaine penicillin products is unnecessary. There are advantages to the hospital as well as to the physician and the patient in the use of procaine penicillin in that the reduction in frequency of injections and ease of cleaning needles and syringes eliminates a great deal of nursing time. Costs per patient to the hospital are also reduced as a result of a reduction in the quantity of the drug necessary and possible shorter periods of hospitalization in those cases where it is necessary.

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Correspondence

Founder of the A.M.A.

To the Editor:

If Thomas B. Wood had read "A History of the American Medical Association 1847-1947" carefully he would not have spoken of my grandfather as the "first president of the A.M.A." In my biographical sketch of "the founder of the A.M.A." I make it clear that he was president for the years 1864 and 1865.

Furthermore in his biographical sketches of all of the presidents, Walter L. Bierring, M.D., who should also have been listed as one of the authors, records N. S. Davis as having served as the sixteenth and seventeenth presidents of the A.M.A., because after his election in '64 it was voted that in the future the president should not be elected until the end of the meeting so that he might be in charge of the plans for the meeting over which he was to preside. Under this change in the Constitution and By-Laws, my grandfather continued in office until the end of the 1865 meeting when his successor was elected.

I have always been surprised that so many seem to be under the impression that because he was largely responsible for the founding of the A.M.A., he must also have been its first president. He was not even

the chairman of the 1846 meeting in New York which adjourned to meet again in 1847 in Philadelphia to found the A.M.A., but was chairman of the committee of the New York State Medical Society that called the preliminary meeting.

N. S. DAVIS III
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To the Editor:

I have read the letter from Doctor Nathan S. Davis addressed to you in criticism of my review of A History of the American Medical Association with a great deal of interest.

Dr. N. S. Davis is absolutely correct in all of his statements. His grandfather was the founder of the A.M.A. and not its first president. He was the sixteenth president.

The error is a natural one as he explains so well in his last paragraph. After reading the book the impression seems to stick in one's mind that N. S. Davis was the founder and first president which of course is not so.

I wish to thank both you and Doctor N. S. Davis III for drawing my attention to this unwitting error so that it might be corrected.

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Fugues in the Preadolescent Period of Life

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A reflex act is the principal law of nervous activity. A pure, simple reflex is automatic. As we advance in our development, new attributes appear and serve the purpose of coordinating or controlling the tendency to direct reflex action. Otherwise speaking, they transform a blind force into a conscious and determined one, viz., into volition.

Impulsive actions are the expression of a reflex phenomenon, consequently they are physiological as long as they remain subordinate to the cortical centers. As soon as this subordinate equilibrium is interrupted, the impulsive acts become pathological.

All impulses may be endogenous, originating from internal motives; they may be strong or imperative, followed rapidly by motor phenomena; they may be aberrant or dependent upon exigencies of life; they may be conscious but difficult for inhibition; finally they may be unconscious. The chief characteristic lies in the unusual rapidity or else the suddenness of the impulsive process, also in its frequent repetition in a paroxysmal manner, finally in the want of parallelism between the degree of awareness or unawareness of the impulsive act and the degree of loss of memory with regard to the impulsive act.

From a clinical point of view impulsive acts may be purely motor, in which the act follows the stimulation immediately; psychomotor, in which an emotional element is intermediary between the stimulation and the terminal act; finally psychic, in which the intermediary emotional element is long, painful and accompanied by an inhibitive force. In the latter form there is lucidity of mind, but the patient struggles, and tries to overcome the irresistible desire.

It would require perhaps a volume to describe all the various manifestations. They are all valuable for diagnostic purposes and particularly interesting from a

psychological viewpoint. Psychoanalysis will no doubt reveal hidden motives and causes for each of them. I will confine myself to a single variety of impulsive acts which I have had the opportunity to observe in children of all ages. Because of its practical interest I shall consider it somewhat fully. I have reference to the so-called "fugues." As we shall see later, the misrepresentation of this phenomenon may lead to gross errors, especially in counseling parents and teachers with respect to the child's present and future. A reservation must be made at the outset of our discussion, namely, that this impulsive phenomenon will not be considered from the standpoint of insanity. Fugues may occur in many psychoses, but my intention is to describe its occurrence in the life of children free from grave mental disorders, in which, of course, the manifestation under discussion is the result of suddenly appearing hallucinatory images or delusional conceptions.

In order to make the subject somewhat lucid a few examples of my cases will be very briefly described:

Case I.—A boy, aged eight, brought up in an atmosphere of gentility and refinement, had three attacks of the same character at intervals of four or six months. The first time he suddenly disappeared over night. He was found asleep under a bridge. The second time he stole one dollar from his mother and ran off. He was found at Broad Street Station. The third time he did the same as the first time. When repeatedly questioned on the motive of his acts, his reply was that an irresistible desire overwhelmed him to test independence. "This sudden idea passed through my head and I could not help myself."

Case II.—A girl, aged six, who had a young mother of twenty-five, whom she

always saw surrounded by admirers, had a tendency to describe dreams of the most fantastic character. She saw herself flying in an airplane or travelling on steamers. She also had frightful dreams, some of which were typical of night terrors. Without an apparent cause she suddenly became morose, seemingly depressed. During a period of two years she made six fugues; would suddenly disappear and for hours could not be found. She would return home by herself, being incapable of giving an intelligent account of her aimless acts.

Case III.—A boy, aged eleven, would suddenly expose his genitalia. A few minutes later he would find himself in this situation, would cry and hide himself, ashamed of his act.

Case IV.—A girl of ten, upon return from school, would suddenly place herself in a position of a teacher, close her eyes and perform serious gestures, calling out names of supposed pupils, reproach them, correcting their supposed errors. At the end of five or ten minutes she would suddenly open her eyes and look around without fully realizing what had occurred. However, in an hour or two she was able to recall some portions of her acts. The amnesia evidently was not complete nor profound.

Case V.—A boy, aged twelve, the only child of a widowed mother, unusually precocious in his mental development, read a great deal, sometimes until three o'clock in the morning. He developed unusual ideas concerning parenthood, filial attachment, and especially the marriage problem. At his tender age he did not believe in marriage; he frequently spoke of personal freedom. On four different occasions he disappeared from his home and each time his reply was that the desire to be free was so overwhelming that he could not resist; he did not plan or prepare himself for the flight; sometimes the idea came in the middle of the night after disturbing dreams.

These five examples are sufficient to illustrate the nature of the disorder under discussion. Our entire series of cases presents an identical picture with some slight variations as to the circumstances in which

the flight was made by the little patients. We can therefore define a fugue as a paroxysmal, impulsive act consisting of sudden abandonment of one's own domicile without a reasonable motive. Another characteristic feature of this act is the irresistibility of the desire to accomplish it, in the midst of preservation of consciousness and memory.

In all fugues the patient is unable to measure or even to consider the consequences. They are not different from other impulsive outbreaks, such as impulse to attack, to destroy, to burn, to tear, to use violence. They are all the final result of obsessive ideas, in which the irresistible desire to carry them out is so overwhelming that the individual succumbs to them without having time to consider either the consequences or the feasibility of such an act. Irresistible impulses of all kinds are observable in children of all ages as well as in adults, but fugues such as described above in the few examples are not frequent.

The object of presenting this subject on the normal and pathological life of children is to call attention to the fact that, while impulsive acts in the form of fugues are observed in young individuals free from serious mental disorders, nevertheless their paroxysmal occurrences have a deep meaning and important significance. Children presenting these episodic manifestations cannot be considered as possessing a well-balanced equilibrium between the constantly arising internal motives and the cortical control. In all such cases the power of inhibition is wanting or defective. Such children form a class of abnormal individuals. Indeed, if one analyzes the personal histories of every one of these cases, one is astonished to find many other peculiarities ordinarily not found in perfectly normal children. Frequently there are evidences of psychological and physiological as well as morphological deviations from normality. Instability, perverted mode of feeling and acting, sometimes affective indifference, apathy toward the nearest or the dearest; sometimes unusual cruelty, extraordinary hostility toward those who never cease to show their

love and affection. A tendency toward deception and lying is not uncommon.

In other cases, on the contrary, we find a normal intellectual development and even one superior to normal, a remarkable power of assimilating, an unusual memory, but alongside of these superior qualities there may be defective judgment and reasoning. In many of these cases we obtain a history of motor or psychomotor disturbances, such as paroxysmal attacks of choreiform movements, and spasmodic muscular contractions, of hysterical manifestations, of night terrors, of enuresis. Many of such children present physical stigmata of abnormality, such as high-arched palate, congenital strabismus, misshapen segments of the body and cranium, etc. When many of the signs of abnormality just enumerated are present, the task for the physician and parents is comparatively easy. In a number of such cases, however, those evidences of abnormality are not conspicuous and may be easily overlooked. In other cases the outward abnormal manifestations are seen grossly in impulsive outbreaks. It is only the repetition of the fugues that arrests the parents' attention. In all such cases the fugues are but one of the many expressions of an abnormal or defective background. Acts such as running away from home aimlessly and without a motive while being surrounded with love and constant affectionate attention, in spite of the ever-present instinct of self-preservation, and repeating the impulsive act again and again without an external provoking cause, perforce originate in individuals in whom the intellectual and affective equilibrium is defective. Psychologically considered, fugues may be viewed as due to an insufficiency or a feebleness of reactive power; in other words, they are reactions of inferior quality expressed as an unconscious defense of the organism against conditions or situations in which the individual lives. It is a procedure of self-isolation with the purpose of becoming detached from the environment in which the individual is living. It is a psychomotor act of an abnormal individual.

Familiarization with such occurrences in

young children will arrest our attention with regard to the management and therapy. Upon the latter depends the future of the child. Once recognition of the phenomenon is made and a proper evaluation is accomplished, necessary measures should be undertaken as early as possible. A supposedly healthy child who has impulsive outbreaks such as previously described, even with the exclusion of any other conspicuous mental manifestation, is to be considered abnormal. His mode of living, his mental development and his emotional life must all have a different direction from that applied to normal life. Parents must be made to understand that children so constituted are perpetually subject to outbreaks of another character besides their fugues; that their make-up is different from that of normal children; that their way of living and their occupational hours must be filled with tasks different from those which we supply normal children; that their cerebration must not be unduly forced or hastened; that their emotional life must be taken special care of; that as the child grows, no definite plans must be made in advance as to a future vocation. In this particular respect it is wise to bear in mind that an occupation associated with great mental effort or with strong emotional features should not be thought of.

The characteristic features observed in abnormal children, such as previously described, particularly those which make their appearance episodically, are the result of emotional conflicts in the unconscious and conscious life. It is therefore important that in the management of such children our main efforts should be directed toward the emotional side of their life. Negligence in this special direction is bound to lead those children in the critical period of life, viz., puberty, to a complete mental collapse, and an incurable psychosis will then make its appearance. On the other hand, if the condition is fully recognized and a proper value attributed to it, those abnormal children may be guided safely to puberty, they may cross this critical period of life, enter adult life sufficiently

—Concluded on page 397

Anomalies of the Thyroid Gland

with Special Reference to the Unilobular Thyroid

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The following report concerns a patient who revealed a large calcified cystadenoma of the right and complete absence of the left, thyroid lobe. There are few references to this anomaly in medical literature. However, there have been a few reports of congenital myxedema in which no thyroid tissue was discoverable, and in which only the epithelial sinus and its outgrowths were present (Spencer⁵, Dieterle², Ungermann⁶, Aschoff¹).

In an attempt at an explanation of this anomaly, it is necessary to review briefly the embryology of the thyroid gland. The primordium of the thyroid gland (median primordium) appears simultaneously with the first pharyngeal pouch when there are ten primitive segments. The primordium develops as an epithelial evagination in the ventral pharyngeal wall dorsal to the tuberculum impar of His and anterior to a prominence formed by the ventral extremities of the second and third branchial arches. In other words, it develops between the first two anterior pharyngeal grooves directly ventral to the area of the second branchial arch. Although the belly of the tongue develops in the area between the first and second branchial arches, the radix linguae takes origin mainly from the prominence which is formed by the ventral ends of the second and third branchial arches (copula) and to a less extent by the tuberculum impar. The thyroid evagination takes origin at the point where the corpus linguae and radix join, later to become the foramen cecum. This thyroid evagination, which elongates caudally (as a result of growth and simultaneous elongation of the embryo), takes the form of a hollow epithelial stalk (thyroglossal duct). During development the stalk-lumen is obliterated, but the stalk

proper persists temporarily as an epithelial cord, with its caudal end developing laterally as a bilobular lumenated structure. This occurs prior to its separation from the pharyngeal lumen. Later, as the lobes enlarge and grow caudally and posteriorly, the lumen becomes obliterated. In this way the isthmus, pyramidal lobe and part of both lateral lobes are formed. The major parts of both lateral lobes, however, are formed by solid lateral outgrowths [His³]. At this stage the mass is composed of irregular transverse cords of cells which become lumenated and break up into separate clusters (the anlage of the thyroid follicles).

The parathyroids, on the other hand, arise from dorsal protrusions of the third and fourth pharyngeal pouches as small epithelial bodies which migrate anteriorly and caudally to take their definite position posterior to the thyroid primordium. The buds arising from the third pharyngeal pouch descend to the lowermost part of the thyroid, while those from the fourth pouch migrate only down to the middle of the posterior surface of the gland.

Myxedema always occurs as a result of failure of development of the median primordium, with consequent absence of a normal thyroid. Here, however, the parathyroids are usually found in their normal position. Although the thyroid isthmus may be absent in as high as 10 per cent of persons, absence of one lateral lobe in its entirety occurs in less than 1 per cent [Marshall⁴]. This is explainable from the viewpoint of embryology on one of two grounds: (1) that instead of the caudal end of the epithelial stalk developing laterally as a bilobar structure, it took the form of only a single-lobed thyroid primordium; or (2) developmental failure of one of the solid lateral anlages

that were destined to form the main substance of the lateral lobes.

Incidence of Variations. According to Marshall (who based his conclusions on observation of 60 children ranging in age from a few weeks to ten years), variations in anatomic configuration of the thyroid gland are extremely common. The pyramidal lobe has been found developed in approximately 50 per cent of persons. In the large majority the lateral lobes are equally developed, while in 7 per cent of those examined, one lobe was distinctly larger than the other. Complete absence of one lobe was noted only once, the gland consisting of the left lobe and isthmus. The isthmus was absent in 6 persons (10 per cent), but in 25 per cent of the group it was fused with one of the lateral lobes.

The pyramidal lobe was found fully developed in 26 children (43 per cent) and attached to the hyoid bone in 7; in 9 it terminated in the fascia covering the thyroid cartilage. Extension of the pyramidal lobe to the isthmus was noted in some, and in others it was found attached to one of the lateral lobes. There was one instance where the lower end of the pyramidal lobe was bifurcated, with a limb connecting each lobe; in another example the pyramid was reduplicated.

The foramen cecum was absent in 38 per cent of persons, while in 46 per cent it appeared as a depression measuring one-eighth inch, and in 15 per cent it measured one-quarter inch in length.

Case Report. Mr. M. S., lawyer; aged 63; noted hard tumor on the right side of neck for at least 15 years. Although always emotional, for past eight or nine years extremely nervous; developed severe tremor of fingers and could not gain weight despite enormous appetite and enjoyment of food. Believes that mass on right side of neck has been slowly but progressively increasing in size. For several years has been advised by his physician to have tumor removed, but was reluctant to do so because of apprehension of any kind of surgery.

The outstanding features of the physical

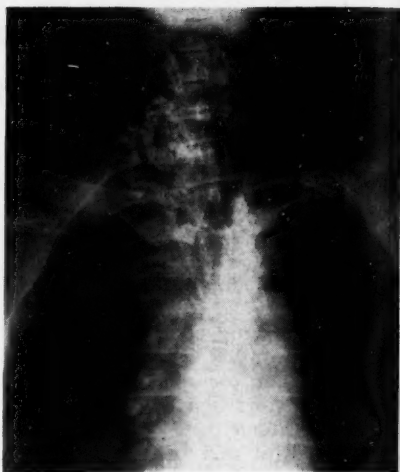


Fig. 1. Roentgenogram showing diffuse calcification of the right lobe of the thyroid.

examination were a fine tremor of the outstretched fingers; blood pressure 150/90; palpable spleen; moderately enlarged, nodular, elastic prostate. Pulse rate 80. Weight $131\frac{3}{4}$ pounds. Examination of the neck disclosed a stony-hard, ovoid mass about the size of a large pigeon's egg, involving the region of the right thyroid lobe. The tumor, while not adherent to the overlying skin, appeared to be attached to the deep structures of the neck. It moved only slightly with deglutition. The left lobe of the thyroid could not be palpated. The thyroid cartilage was enlarged and extremely firm.

Roentgenographic examination of the neck showed an irregularly calcified mass involving the right lobe of the thyroid. It did not extend into the superior mediastinum. (Fig. 1).

Laboratory Data: Blood count: hemoglobin 108 per cent; red blood cells 5,400,000; white blood cells 8,400; color index 1.0; polymorphonuclear leukocytes 64 per cent; lymphocytes 36 per cent. Sedimentation rate: 8 mm. after one hour.

Urinalysis negative.

Blood chemistry: sugar 96.4 mgm. per

cent; calcium 10.0 mgm. per cent; phosphorus 3.1 mgm. per cent; cholesterol 153.0 mgm. per cent.

Bleeding time 2.45 minutes; coagulation time 6.15 minutes.

Basal metabolism 21½.

Presurgical diagnosis: Calcified adenoma, right lobe of thyroid gland.

Operation (Nov. 11, 1947). Under avertin and gas-oxygen anesthesia the thyroid gland was exposed through a low collar incision. Involving the entire right lobe of the thyroid there was a hard, calcified tumor about the size of a large pigeon's egg. It was firmly adherent to the surrounding structures, including the string muscles of the neck. The left lobe of the gland was absent, although the parathyroids, which appeared slightly enlarged, were in their normal positions. The larynx and upper part of the trachea appeared firm and moderately enlarged.

The anterior margins of both sternocleidomastoid muscles were freed, and the string muscles were separated in the midline and divided between clamps in close proximity to the thyroid cartilage. The right lobe of the thyroid was then carefully dissected from below upward. The superior thyroid vessels were doubly ligated and divided, and the tumor was then easily separated by sharp dissection from a small remnant of thyroid tissue forming the posterior rim of the residual right lobe. After thorough hemostasis, the string muscles were sutured with fine chromic mattress strands and then approximated in the midline with interrupted ones of fine catgut. A small Penrose drain was placed in the cavity remaining after the tumor was removed. The skin was closed with Michel clips.

Convalescence was uneventful, and the patient was discharged from the hospital Nov. 15, 1947.

Pathologist's Report: "Macroscopic: Specimen consists of an enlarged lobe of thyroid measuring 7.5 x 5 centimeters. It is well encapsulated. On section it is almost completely occupied by a well encapsulated hen's egg-sized, solid and cystic tumor which contains a moderate amount of colloid and shows severe interstitial hemorrhages and fibrosis, and great calcification. No parenchymal capsule is present.

"Microscopic: Tissue is encapsulated. It contains regular thyroid alveoli of varying size. They are lined by flattened cuboidal cells and contain scant colloid. There are broad areas of hyaline fibrosis and interstitial hemorrhage. Calcification is present. There is a thin zone of atrophic colloid containing thyroid parenchyma.

"Diagnosis: Hemorrhagic, calcified cystadenoma of thyroid."

Conclusion

This report deals with an example of congenital absence of one lobe of the thyroid gland, and a calcified hemorrhagic cystadenoma of the remaining lobe. Congenital absence of one lobe of the thyroid is a rare anomaly, occurring in less than one per cent of persons. There is a brief review of the embryology of the thyroid gland and its anatomic variations.

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Women Past 49 Respond Best to Treatment for Cancer of Cervix

Women past 49 respond more favorably to treatment for cancer of the cervix than

do younger women, physicians of the Mayo Clinic, Rochester, Minn., have found in a study made of 3,798 patients at the clinic from 1915 through 1944.

Thoughts on Liver Dysfunction

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For many years clinicians have attempted to find a liver function test which would give a clue to early changes in this organ. None so far have been found satisfactory. The reason for this failure resides partially in the tremendous reserve in the liver cells but also because of the large number of functions of the liver. Professor Ivy during a series of lectures remarked that 80 different liver functions are now recognized. This multiplicity of functions practically precludes any test which could give adequate information regarding the state of the liver. It will always, therefore, be necessary to use clinical observations and judgment in determining the state of the liver and to evaluate the part played by this organ in any clinical syndrome.

It is with this in mind that I am undertaking to call attention to a few clinical observations which have been helpful during the past few years. Some years ago the writer called attention to a unique clinical syndrome,¹ consisting of drowsiness, vertigo, diplopia, speech disturbances, changes in reflexes and increase in spinal cytology. This syndrome was present in certain patients who proved to have chronic biliary tract infection, with or without stones in the gallbladder.

Some of these patients improved or recovered under conservative management, but many were operated upon, the gallbladder was removed and prompt recovery ensued with disappearance of all of the above symptoms. The writer did considerable speculating as to the nature of this syndrome and the factors which caused the neuropathy. Why did some patients with biliary tract disease develop this syndrome while the majority did not? The question of neurotoxins, allergy due to breakdown of liver cells and other possibilities

were considered but no definite answer was found.

However, as the clinical picture of vitamin deficiencies became more clear, the picture of acute riboflavin and niacin deficiency came to resemble very closely the syndrome seen in the case of biliary tract disease with neuropathy.

The cases seen subsequently were then subjected to intensive vitamin therapy and the neuropathy was relieved. The biliary tract infection could then be cared for conservatively and only rarely is surgery now required in these cases.

This brings us to the core of the subject in my mind at the moment. Is the hepatic disarrangement the cause of the vitamin deficiency or is the vitamin deficiency an accidental association?

My own opinion, based entirely on clinical observation, is that the conditions are intimately related. The liver is probably very important, in some way not yet made clear, in the metabolism of vitamin B factors, and in some case of biliary tract infection there seems to be an actual inability to utilize these vitamins, or the body requirements increase so greatly that the picture of acute shortage of riboflavin and niacin develops.

That this difficulty is not limited to the above-mentioned cases alone is made clear by the frequency with which the more classical types of vitamin B complex deficiencies are seen in connection with biliary tract disease. It is very common to see glossitis and cheilosis in patients with gallstones even when it can be determined that the patients are on adequate diets.

This occurs even when there is no hypochlorhydria or achlorhydria, which of course is known to destroy much of the vitamin B factors. It is often impossible to clear up the glossitis except by giving very large

doses hypodermically, together with the natural vitamins by mouth.

The synthetic preparations do not seem so effective here as yeast powder or other natural vitamins. There are other conditions within the mouth which seem occasionally to be related to disturbances in the functions of the liver.

I have seen stubborn cases of leukoplakia of the tongue associated with gallstones. Usually no response is obtained under any form of treatment until the gallstones are removed and then large doses of yeast powder bring about restoration of the normal condition of the tongue.

Recently I had a new experience along this line. A patient was seen February 6, 1945 with lesions of pemphigus in the mouth and tongue which had been present for five months. The diagnosis of pemphigus was verified by Dr. Arthur Curtis of the University of Michigan.

She did not respond to any form of treatment. She then began to have attacks of gallstone colic and surgery was done on July 11, 1945. The mouth lesions cleared and except for a mild return of a few spots under the tongue, the patient has been free from recurrence. Weight increased from 136 to 156.

Since pemphigus of the mouth carries

with it a fatal prognosis, usually in less than two years, and this patient is still well (it is 2 years since onset of the lesions), another possible association is uncovered by this experience and the biliary tract and liver must be given greater consideration in this usually fatal disease. Incidentally, following non-surgical biliary drainage with the duodenal tube, the few vesicles under the tongue, mentioned above, cleared immediately.

My purpose in writing this paper is to call attention to the great and still unrecognized influence of disturbances in liver function on the general health of the individual and to stimulate greater clinical studies of these problems.

The laboratory is not yet able to solve these problems for us, and unfortunately in these days of scientific investigation we are too prone to refuse to accept clinical observations which cannot be verified by the laboratory.

I feel that clinical observation often must precede and suggest the line of investigation for the laboratory.

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1838 PARKWOOD

MISCELLANY

PROCEEDINGS OF THE PICKWICK CLUB

The *Congressional Record* recently carried some remarks made on the floor of the Senate by a member of that body and now printed broadcasts of these remarks are reaching many physicians. These remarks were allegedly made in the interest of the health of the American people. They were made on June 7, 1948, and highly endorsed a well known cancer "cure."

In the course of the Senator's remarks the two following cases were reported and the A.M.A. scored for its skeptical attitude:

However, my father did have my sister treated, since he personally knew of cases of cancer which were cured and remained cured after its use. This type of cancer is fatal in 3 to 6 months, as a rule.

My sister was in the last stages and was said to have only a few weeks to live, according to the best knowledge on the subject. She recovered after one dose in characteristic fashion.

One leading breeder told how the Koch treatment had saved an especially good cow given up to die. He explained that it developed mastitis during lactation. A veterinary surgeon advised him to have the animal removed from the herd and slaughtered. There was danger of the infection spreading.

Instead, the Koch treatment was applied. The action consisted of one dose of the therapeutic agent being administered by hypodermic syringe under the skin of the neck. Recovery was instantaneous and within a week the cow's milk was being sold to the creamery.

Atypical Appendicitis

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According to Sloan, the anatomic recognition of the appendix dates from the pyramids. As early as 1759 Mestivier performed an operation for appendicitis. Kronlein removed the first appendix in 1884, while Hall, in 1886, was the first American to remove a gangrenous appendix. Reginald Fitz in 1888 gave to the medical profession the diagnosis of appendicitis. Just as fifty years later Fitz, the younger, wrote of the "challenge of appendicitis," as it existed then, so it exists today. While the literature of appendicitis is the most extensive of any disease, and the medical profession individually and collectively has had more experience with appendicitis than any other disease, there are many cases that are undiagnosed before they become a serious surgical problem. Alvarez, who a few years ago reported a series of patients whose appendices had been removed with no change in the picture, has rendered a distinct disservice to the profession as well as to the general public in as much as this proves nothing as far as the appendix is concerned. Wangenstein and Wilkie are responsible for the statement that appendicitis may exist without fever, pain or leukocytosis, that acute appendicitis at the start is non-inflammatory, only obstructive.

A classical diagnosis of appendicitis with the sequence of abdominal pain, nausea and or vomiting, localized pain, rigidity, fever and leukocytosis is within the knowledge of the mere tyro in medicine, but many of the atypical cases tax the knowledge, experience and skill of physicians of mature judgment. Appendicitis must be differentiated from pelvic inflammations, ruptured ectopic pregnancy, twisted ovarian cysts, ruptured ovarian follicle, small pedunculated fibroid, renal lesions such as ureteral colic, ureteral kink, intermittent hydronephrosis; diseases of the upper

abdomen, such as ruptured peptic ulcer, biliary colic and pancreatitis. Lymphadenitis is not infrequently mistaken for appendicitis. Acute gastro-enteritis may exist with appendicitis. Diabetic coma may also exist with or without appendicitis. Pneumonia or pleurisy, especially in infants and children, often enters the picture. Visceral crises of tabs are not infrequently a problem connected with the differential diagnosis of appendicitis. Whether or not trauma can produce acute appendicitis is still an open problem for discussion. Meckel's diverticulum, undescended right testicle, phlebitis of the right iliac vessels, cancer of the cecum and volvulus are also conditions that often obscure the diagnosis. Acute bacillary or amebic dysentery does not rule out the diagnosis of acute appendicitis. Worms, especially pin worms and round worms, are commonly found in the appendix. Many patients with appendicitis do not vomit. Some have so little nausea that only a careful history reveals it. The abdominal pain often begins in the right lumbar region. When the appendix is retrocecal, often deep palpation elicits no pain. Not infrequently the painful response may be in the region of the pancreas or the liver. The appendix may be transposed or pulled to the left side, causing pain and rigidity on that side. An appendix may lie deep in the pelvis; only rectal or vaginal examination reveals the condition. It may be attached to the bladder, causing the classical bladder pains. The presence of blood in the urine does not rule out the diagnosis of appendicitis. A gangrenous appendix is not infrequently found in a right inguinal hernia sac. As a matter of fact, appendicitis may exist with any one or more of the many conditions previously mentioned.

A careful physical examination with every possible laboratory aid should be the practice of every physician. If a

reasonable time is allowed to elapse before operation, as a rule localization will guide the surgeon to the appendix. Often time will clear the whole picture, making an operation unnecessary. However, if there is any possibility of appendicitis being present, the decision should be made in favor of immediate operation. This is a well established principle of surgery which is and rightly should be practiced by every surgeon. With our present surgical technique, safe anesthesia and antibiotics, it is far better for the patient to have a normal appendix removed than to run the risk of the serious consequences of unnecessary delay. Exploratory laparotomy is a well recognized procedure. Often the unexpected is discovered and the patient's life is saved.

While within the past few years the mortality from appendicitis has been greatly reduced because of the diagnostic acumen of the physician and the skill of the surgeon, many lives are needlessly sacrificed because the mental picture of this disease does not include the atypical forms. Fever, leukocytosis and pain are not necessarily the indicators of the seriousness of the condition. Often one is surprised to find a severely diseased appendix which has not been indicated by the physical and laboratory findings prior to opera-

tion. The reverse holds true also.

The most constant, in fact the only symptom of appendicitis that is always present is pain in the abdomen. Any abdominal pain should be viewed with suspicion until it can be proven harmless. Whether or not it is accompanied by fever, whether there is constipation or diarrhea, the possibility of appendicitis always exists.

While the dangerous use of purgatives has well nigh passed into oblivion, still they are often administered not only by laymen, but are thoughtlessly prescribed by physicians. A well known dictum that a purgative can never do a bellyache good, but may do much harm, cannot be stressed too often.

To attempt to differentiate the acute appendix from all other conditions found in the abdomen is beyond the province of this paper. Many textbooks deal with the subject clearly and exhaustively. Suffice it to say that the possibility of an acute appendicitis should always be considered whenever one is confronted with a painful abdomen.

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701-5 MEDICAL ARTS BUILDING



FUGUES IN PREADOLESCENCE

—Concluded from page 390

prepared to meet obstacles, and at the same time be of some use to the community. The early appreciation of unusual manifestations in children, no matter how slight the latter might be or how isolated they may appear, will lead to proper conduct in therapeutic management. Upon such a diagnosis the prognosis and prophylaxis depend entirely.

Not infrequently an analysis of a single abnormal phenomenon will gradually lead to unearthing other important features which, all combined, will present a structure requiring our serious attention.

I have endeavored to present for thoughtful consideration a subject which is full of deep significance. It deals, it is true, with one phase of human behavior, but when analyzed it leads us in an ascending manner to a deeper insight of a child's constitutional make-up, the recognition of which may be rich in fruitful results. Clinically speaking, it establishes the proper diagnosis, prognosis, and management. The entire subject presents a very important problem not only for the physician but also for the parents. Recognition and proper evaluation of any abnormal phenomenon in children constitute a very instructive chapter in mental hygiene.

1520 SPRUCE STREET

EDITORIALS

"Nationalyphilis"

Representatives of the magazine *Life*, roaming recently through Yugoslavia, report that the doctors are subject to arbitrary orders to proceed anywhere the government wishes them to go. One can easily imagine how such complete control in a totalitarian regime operates *politically*, since power of this type is bound to be abused.

Lewis J. Moorman, editor of the *Journal of the Oklahoma State Medical Association*, reminds us in the June issue of that publication that Bismarckian policies in Germany were what ultimately made mass murderers of many of Hitler's doctors. How, asks Doctor Moorman, can we expect the same or even similar policies to make angels of us?

Yet the proponents of nationalization in this country promise to solve all our medical problems by means of their miraculous panacea. The European experience, past and present, is lost upon them; to them its fetid odors are as roses and honeysuckle. It is a spiritual sickness which in this case prevails here—America's first public health problem!

Political Medicine in Britain

The so-called liberal press has a glib explanation of the new British brand of socialized medicine. When British *wealth* was derived from foreign investments poverty and sickness at home didn't matter much; now labor at home must be taken care of if production is to be increased and national income maintained. But mediocre care under a paternalistic system is a dubious project. Under either the old or the new system the worker is gypped by the politicians. Besides, the British can not afford it (unless our aid is to make it click for awhile).

Canadian Family Aid

Canada's family aid system has increased



medical and dental attention, school attendance, and the consumption of milk, cod liver oil and children's clothing. This program has been in effect three years and involved an expense of about \$20,500,000 a month. The average family allowance

is a little less than \$14 per month, allotted to 1,675,000 families involving 3,775,000 children. The allowance is received by all families who apply and who meet a few very simple eligibility requirements. Eighty-four per cent of the children are found in the homes of 19 per cent of the wage-earners.

The average payment of somewhat less than \$14 per month per family represents a 10 per cent increase in the average family income, from which the inadequacy of the Canadian wage structure may be inferred. This addition to the wage by the government raises the family to a bare subsistence level.

Canadian sponsors of the system have been somewhat mystified by the failure of American welfare workers to show any interest in it. We think this failure may possibly be accounted for by the fact that the system is intended to influence the birth rate, which latter is effected by decreasing the scale of allowance from the fifth child on. This would seem to be too "leftish" a method for federal administration in the United States, Canada seems to lean a little to the totalitarian side, as witness the socialization of medicine in Saskatchewan.

Of course the lowering of the scale of allowance from the fifth child on also takes into account the possibility of parents making large families the sole source of income.

All such schemes as this possess a specious attractiveness. The basic pathology, of course, is the wage structure. The families aided by the politicians can not make ends meet.

As was said editorially in our June issue, the shift from free enterprise to socialism is a function of poverty; the promotion of general poverty makes for totalitarian control. The ideal of the collectivist is a state in which general poverty is attained and shared. The degree to which the private practice of medicine is opposed is a measure of communistic trend. The medical profession should interest itself more in the maintenance of a decent wage structure.

A Therapeutic Paradox

Strangely enough, both Dicumarol and vitamin K give favorable results in acute coronary artery occlusion; yet their effects upon the blood are opposite in nature, the one increasing the tendency toward clotting of the blood, the other lessening it.

Doles, proponent of vitamin K, claims that hypoprothrombinemia is the rule in occlusion [*Southern Med. J.* 40:965 (December)]. It appears that the pain is due to hemorrhage beneath the intima, much as in the case of pain observed in a dissecting aneurysm of the aorta. Doles reports a rise in prothrombin time with corresponding relief of pain in less than three hours as a result of prompt vitamin K therapy.

There has been no clear explanation of

this therapeutic paradox. It has been suggested that the differing results may be due to differing factors—that as there is no simple type of occlusion so there can be no rigid therapy. At any rate, sharp indications can not at present be set down.

But there is no likelihood that any clinician who has gained fame in this field will ever find himself in the position of Henri Poincaré when he was awarded the Nobel prize for a paper that contained a serious mathematical error.

The National Hospital Construction Program

The United States Public Health Service announced, in July, 347 projects in forty-two states under the national hospital construction program authorized by the Hill-Burton act, with the Federal Government paying one-third of the costs and the states and local communities two-thirds. The 347 projects, when completed, will add 11,846 general beds to our facilities at a total cost of \$160,734,258. Even some rural counties in poor states are participating. The hospitals seem to range in capacity from 25 to 200 beds. One 47-bed hospital cost about \$463,000 to erect; such a hospital costs from \$58,000 to \$96,000 to equip.



LICHEN PLANUS

—Concluded from page 376

to its being allergic or due to spasms of the peripheral circulation such as might be produced by physical or chemical insults.

The query of Dr. Beck on page 178 of the *Journal of the American Medical Association* for September 8, 1945 as to a possible relationship to gout and therefore amenability to colchicine indicates a possible line of approach.

The case reported herein is confessedly atypical, but it does show the development of lichen atrophicus in a lesion biopsied by one of the leading dermatologists of this country.

It does show also the ineffectiveness of

salves and lotions (except to relieve the itching) and of the internal remedies suggested.

It made me believe that the basis of the disorder was vasomotor; that is, that it was akin to peripheral vascular disease. Therefore if I had to suggest treatment for a similar case, and could see it early, I would set up a program of local hydrotherapy and massage (including the alternation of heat and cold). I would try to stabilize the general circulation by the use of such drugs as aminophyllin—and I would not fail to investigate the influence of tobacco on the peripheral circulation of that particular patient.

And, finally, if the lesion has become fixed, I would consider plastic surgery.

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GENERAL PRACTICE

When Sleepers Awake

Failure of the general practitioner majority of the profession, until now, to organize in the interest of its own welfare finds something of a parallel in the failure of consumers, until recently, to organize similarly. The tremendous latent power in each group long laid dormant in the face of outrageous abuses.

Of course, the organizations are not complete. Even yet, only a small proportion of the highly individualistic general practitioners have joined the American Academy of General Practice, though it is growing apace.

The potentially all powerful consumers (everyone is a consumer), although practically all their income is consumed in exploitative living expenses, dumbly resist organization as such, that is, as consumers. They are seemingly unable to realize that they are consumers before they are anything else and that the government and political parties do not represent them as such.

It has been suggested (*New York Times*, July 19, 1948) that there should be a consumer movement as strong at least as the labor movement in order to make our system work more equitably.

Let us hope that the movement now ably sponsored by general practitioners in their own behalf, as well as the consumer movement, will go forward with increasing momentum.

The "Central Figure" of the Medical Profession Marches On

As has been stated by the Joint Committee for Coordination of Medical Activities, "there is an immediate need for integration of general practitioners into hospital staffs throughout the country." Graham Davis, president of the American

Hospital Association, said, "I think it would be the general policy of the American Hospital Association to say that every reputable physician should have a hospital staff appointment."

—Wingate M. Johnson, M.D.
in *J.A.M.A.*, July 10, 1948.

University of Michigan Offers Residencies in General Practice

More general practitioners to care for the needs of rural areas in Michigan is the goal of an experimental two-year residency program being inaugurated by the University of Michigan Medical School.

Writing in the July 10 issue of *The Journal of the American Medical Association*, Charles F. Wilkinson, M.D., of the University of Michigan Medical School, Ann Arbor, says that the program has the approval of the Council on Medical Education and Hospitals of the American Medical Association and of the Michigan State Board of Registration in Medicine.

The first year of the program will consist of six months of internal medicine, dermatology, and surgery, and six months on medical and surgical services, to include obstetrics, psychiatry, neurology, dermatology, other nonoperative specialties, and all the operative specialties, according to Dr. Wilkinson.

The second year will be spent on obstetrics and gynecology, neuropsychiatry, pediatrics, and medical and surgical services, "with a possible third year," he says.

"Many areas in Michigan were not being covered by doctors and in some cases, large numbers of people have no medical care or else have been subjected to the care of an osteopath. In many areas, older physicians are retiring and no younger men are coming to take over the practice of these elderly physicians," Dr. Wilkinson points out.

CONTEMPORARY PROGRESS

PEDIATRICS

Effect of Influenza Virus Vaccination in Infants and Children, with Antibody Studies

P. Cohen and H. Schneck (*Journal of Pediatrics*, 32:161, Feb. 1948) report the subcutaneous vaccination of 100 children from one month to eighteen years of age with a vaccine containing inactivated influenza virus, type A and B, adsorbed on calcium phosphate. The dosage was $\frac{1}{4}$ cc. for children up to three years of age, $\frac{1}{2}$ cc. for those three to six years of age, $\frac{1}{2}$ to 1 cc. for those six to twelve years of age, depending on the size of the child, and 1 cc. for children over twelve years of age. Reactions were mild in most children, consisting of some local soreness at the site of injection; 4 children had a slight febrile reaction with a rise of temperature to 100 to 100.6° F., and one showed a higher temperature (102° F.). Nodules developed at the site of injection in 8 cases, but persisted only a short time. A second injection of vaccine was given to 22 children without causing any systemic reaction. The vaccine was given to some children with a history of allergy but not to any child with a history of egg allergy, because the influenza virus is cultivated in the chick embryo allantoic sac. The average antibody response in children over two years of age was a rise in titer from 7 to 23 times the prevaccination level, comparable to the response in adults. In some cases the antibody response was uneven, in that some did not produce antibody against one of the strains of virus, although producing antibody against the other strain. There was no significant antibody response in children under two years of age as has also been observed by other investigators. A widespread epidemic of influenza that was anticipated in the winter of 1946 to 1947 did

not fully materialize and the number of cases of influenza was far below expectancy. In a control group of 200 children of similar age that had not been vaccinated, 19 cases of influenza occurred, an attack rate of 9.5 per cent, while in the group of 100 vaccinated children, there were only 3 cases, an attack rate of 3 per cent; 2 of these 3 cases occurred three months after vaccination, and one seven weeks after vaccination.

COMMENT

Passive immunization against influenza adds something to our medical armamentarium in the prevention of respiratory disease. We have much to learn about the subtypes of influenza virus. Epidemics vary in their character, the intensity of symptoms and complications from year to year.

Virus vaccine was more effective in the epidemic of 1946-1947 than in 1947-1948, apparently due to a different strain in the latter winter. Immunization lasts from three to four months and it is advisable to give one dose in the fall and another in midwinter to secure the best results. Sterile abscesses do appear in some cases. H.E.U.

Epidemic Poliomyelitis in Children: Clinical Study with Special Reference to Symptoms and Management of Bulbar Poliomyelitis

C. A. Grulee, Jr. and T. C. Panos (*American Journal of Diseases of Children*, 75:24, Jan. 1948) report a study of 464 cases of poliomyelitis seen in the pediatric service of the University of Minnesota Hospitals during an epidemic of the disease in Minnesota, in July to December 1946. In cases in which a history of the prodromal stage was obtained, the chief symptoms were fever, malaise and headache; headache was mild at this stage. Symptoms of upper respiratory tract infection were not as frequent as might have been expected. Symp-

toms of invasion of the central nervous system were more severe and prolonged, including fever, malaise, severe and persistent headache, repeated vomiting, often projectile, constipation, pharyngitis, pain in the neck and back and sometimes pain in a single extremity. This localized pain did not necessarily indicate the site of the subsequent development of paralysis. Bulbar paralysis developed in an unusually high percentage of these cases (23 per cent). The usual initial symptom of bulbar involvement was a nasal twang in the voice or hoarseness, increased accumulation of mucus in the oropharynx, or difficulty in swallowing. Determination of the blood pressure of 70 cases of bulbar poliomyelitis showed definite hypertension in 51, or 72 per cent. The most essential factors in the treatment of the bulbar type of poliomyelitis is prevention and treatment of hypoxia by interrupted aspiration of accumulated secretions, tracheotomy, when indicated, and the administration of oxygen by the respirator or by other methods. As a rule oxygen was given prophylactically when any signs of bulbar involvement developed, until the progress of the case could be appraised. All the deaths in the entire series occurred in the group with bulbar involvement; in all but one case, death was attributed to central cardiorespiratory failure. The surviving patients in the group with bulbar involvement, with few exceptions, recovered completely.

COMMENT

Every physician should acquaint himself

with the symptoms which lead to the suspicion of bulbar poliomyelitis. This severe form is so serious that it needs early treatment.

H.E.U.

The Clinical Use of Penicillin in Oil and Beeswax in Pediatric Practice

F. M. Adams and F. G. Fisher (*Bulletin of Johns Hopkins Hospital*, 82:373, March 1948) report the treatment of 100 cases of pneumonia and 80 cases of other infections in children with penicillin in peanut oil

and beeswax (P. O. B.). Only children with severe pneumonia were hospitalized. All patients were given 5,000 units of penicillin per pound of body weight at each daily injection; daily injections were continued until the clinical response was adequate and the temperature was normal; two more daily injections were then given, and the child kept under observation for another week. In the series of 100

cases of pneumonia, 32 of the children were under twelve months of age; pneumococci were obtained by culture from the nasopharyngeal secretions in 78 cases, sometimes with beta hemolytic streptococcus. In 92 of these cases, the response to treatment with P. O. B. was good; in 81 of these cases symptoms subsided rapidly, in 11 more gradually. In 4 cases the original pneumonia cleared up, but the response to therapy was unsatisfactory because of complications, otitis media in 3 cases and infected adenoids in one case. In 4 cases the P. O. B. treatment failed, because of some complication; these patients subse-

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	Physical Therapy
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Brooklyn, N. Y.	
Harold R. Merwarth	Neurology
Brooklyn, N. Y.	
Earle G. Brown	Public Health
	including Industrial Medicine
Mineola, N. Y.	and Social Hygiene
Henry E. Utter	Pediatrics
Providence, R. I.	
E. Jefferson Browder ...	Neurosurgery
Brooklyn, N. Y.	

quently responded well to sulfadiazine, aqueous penicillin, or a secondary course of P. O. B. There were no deaths. In the 80 cases of other types of infection treated with P. O. B., 27 were cases of suppurative otitis media, 9 of which had not responded to sulfadiazine. There was only one failure with P. O. B. in these 27 cases. In the entire group of 80 cases, this was the only case in which P. O. B. failed; in 6 other cases the response was poor, and in 73 cases good. There were 2 cases in which a mild inflammatory reaction occurred at the site of injection; no allergic reactions occurred. In some of these patients, subsequent intracutaneous injections of aqueous penicillin and of the oil-beeswax vehicle showed no evidence of acquired sensitivity.

COMMENT

The use of penicillin in pneumonia is so well established that little comment is necessary. Penicillin in beeswax has the advantages of being given in one daily dose rather than at frequent intervals, so distasteful to the child, and also it may be given in the home for cases not really needing hospitalization. In severe cases it must not be forgotten that the sulfonamides in conjunction with penicillin produce the best results. H.E.U.

Cerebral Complications in Pertussis

A. M. Litvak and associates (*Journal of Pediatrics*, 32:357, April 1948) report that in 6,002 cases of pertussis seen at the Kingston Avenue Hospital, Brooklyn, in a fifteen year period, 47 showed cerebral complications. In 1932 to 1938 inclusive the general mortality rate for pertussis was 9.4 per cent, and in 1939 to 1946 inclusive, 3.3 per cent. This drop in mortality rate is attributed to the use of sulfa drugs, hyperimmune serum and penicillin. The use of these therapeutic agents did not reduce the mortality in cases with cerebral complications. Of the 47 patients with cerebral complications, 19 died, a mortality rate of 40.4 per cent; 60 per cent of these 47 patients were under two years of age. In 72.5 per cent, the onset of cerebral complications occurred between the third and fourth week of the disease; the usual symptoms at onset were a sudden rise in temperature and convulsions that were continuous or re-

current. In some instances death occurred during the convulsive period; in others, the child became listless, drowsy and stuporous and various neurological signs became manifest. Studies of the spinal fluid were made in 38 of the 47 patients. In all cases the spinal fluid was sterile on culture; and the findings were normal in all but 8 cases. Of the 28 surviving patients, 12 have been followed up for periods of two months to eight years; 6 are living and normal; one was normal for a period of ten months, and died of acute encephalitis of unknown origin (autopsy report); 5 showed some central nervous system sequelae, with a tendency to recovery in 3 instances. Pathological study of the brains of 39 infants and children dying of pertussis showed a complicating meningitis in 4 cases and a glioma of the brain in one case. Pathologic changes attributable to pertussis were found in the remaining 34 brains, and in 17 of these cases a clinical diagnosis of pertussis encephalopathy had been made. Congestion and edema of the brain were present in all 34 cases, petechial hemorrhage in 19 cases, subarachnoid hemorrhage in 3 cases and thrombosis in 2 cases. There were no changes of an inflammatory nature. The term encephalopathy designates these pathological changes correctly. Treatment of cerebral complications in pertussis is symptomatic; no specific therapy has been found to be effective.

COMMENT

Cerebral complications of pertussis appear in the first four years of life. Pertussis vaccine as a preventive has been used since 1934. There is no longer any doubt of the efficacy of this procedure. Protection lasts approximately four years and a stimulating dose at that time continues the immunity as does each contact with the disease in the protected child. It is time that the medical profession recommended immunization for all infants and young children. Cerebral complications could then be prevented. Most of these cases become life long state wards at unnecessary expense. H.E.U.

Rice Sensitivity in Children

L. Slobody and associates (*Archives of Pediatrics*, 65:183, April 1948) find in a review of literature that allergic symptoms are rarely attributed to rice. In a study of

174 unselected children, skin tests with rice protein extract gave a definitely positive reaction in 2 cases, and an equivocal reaction in 6 instances. However, none of these children, not even those with a positive or equivocal skin test to rice protein,

showed any allergic reaction to a diet containing large amounts of cooked rice. It appears that children who are potentially allergic to rice tolerate it well when it is "denatured" by cooking in the presence of moisture.

OTOLOGY

Audiometry with the Use of Galvanic Skin-Resistance Response: A Preliminary Report

J. E. Bordley and associates (*Bulletin of Johns Hopkins Hospital*, 82:569, May 1948) report that an instrument has been developed, under the direction of Dr. Curt P. Richter in the Psychobiologic Laboratory of the Phipps Psychiatric Clinic, which records the activity of the sympathetic nervous system in response to acoustic stimuli. With this instrument the test involves stimulation of the subject by pure-tone signals from a standard audiometer, using faradic shock or other suitable stimuli as a conditioning agent. A recording milliammeter amplifies and charts the responses of the sympathetic nervous system to the test signals, from which a standard audiogram of pure-tone thresholds can be plotted. This test has been used successfully for the entire range of the standard audiometer. Further work is being done with this instrument to define the test procedure still further, and to adapt it for speech audiometry. An objective test of the threshold of auditory activity has long been desired by otologists, but is especially necessary for determining the hearing threshold of infants and young children.

COMMENT

This would seem to depend upon the development of a conditioned reflex and is still a project for the research laboratory. L.C.McH.

A Contribution to the Question of Otitis Media in Infants

A. Mares (*Journal of Laryngology and Otolaryngology*, 62: 207, April 1948) reports that in 101 infants under one year of age

in whom myringotomy was done because the tympanic membrane showed some abnormality, the findings in 6 cases were normal, and the slight changes in the ear drum were attributed to the early age of the infant in 3 cases and to a previous otitis media in one case; in 2 cases the slight injection of the drum around the manubrium was not caused by otitis media. In 16 cases, the slight changes in the ear drum were attributed to a previous "otitis media neonatorum hyperplastica." In 79 cases otitis media was present; spontaneous perforation of the ear drum had occurred in only 9 of these cases; 43 showed only slight changes in the ear drum (slight dullness and/or absence of the cone of light). In 46 cases there was bronchopneumonia or other airborne infection; in 41 cases severe gastro-enteritis; and in 5 cases slight gastro-enteritis. Mastoidectomy was done in 11 cases; there were 3 deaths in this group, due to meningitis with septicemia in one case, and to severe toxemia in 2 cases. The average number of myringotomies in the ears treated for otitis media was 1.8; in the majority of cases, there was definite improvement after myringotomy. Both penicillin and the sulfa drugs proved less effective in the treatment of otitis media in these infants than in older children and adults. In 64 of the 79 cases, the otitis media was cured and the patients recovered; 2 infants died after the otitis media was cured; 8 died from other organic lesions (as proved at autopsy), the otitis media playing only a minor note; 5 died from otitis media and its complications, including the 3 deaths after mastoidectomy, and 2 deaths in infants seen only twenty-four hours before death.

COMMENT

The fundamental indication for myringotomy is still evidence of pressure or abnormal secretion within the middle ear. Mastoidectomy may need to be done upon lesser evidence of mastoiditis in infants with gastroenteritis than in infants who are otherwise well.

We decry a tendency in this country to delay or avoid myringotomy for bulging ear drums in the hope that penicillin or sulfonamide therapy will bring about resolution of the middle ear abscesses. L.C.McH.

The Fenestration Operation: A Survey of 500 Cases

H. P. House (*Annals of Otology, Rhinology & Laryngology*, 57:41, March 1948) reports 500 cases in which the fenestration operation was done more than six months before. The original Lempert nov-ovalis technique with slight modification was used; the cartilage stopple, the gold burr and the more recent lead burr technique were not used in any of these cases. The fenestra was completed in a completely dry field without either intermittent or constant irrigation. The double blue line (or twin bed) technique was used to create the fenestra. The fenestration operation is indicated in cases of progressive deafness of the conduction type in which the patient's general health is good and there is good cochlear nerve function. If the ear drum is intact, a previous middle ear, or even mastoid infection is not a contraindication to operation. While there is no exact method of determining cochlear nerve function, repeated audiometric tests with a 1024 magnesium alloy tuning fork have been found to be reasonably accurate indicators of cochlear nerve function. Patients are tested in a partially soundproof room. Each patient is also tested in a completely soundproof room by an audiologist. The results in the two offices have been found to be quite consistent. On the basis of the cochlear nerve tests, the ideal case for the fenestration operation is one in which the cochlear nerve loss does not exceed 10 decibels in the speech frequencies; the borderline case is one in which the nerve loss is not over 20 decibels in the 512 and 1024

frequencies and not over 30 decibels in the 2048 frequency; any greater cochlear nerve loss renders the case non-suitable for surgery as a rule. Operation has been done, however, in a few so-called non-suitable cases, especially in young patients showing a rapid loss of both air-conduction and cochlear nerve hearing; in such cases the operation may prevent further nerve deterioration. As a rule operation is done on the poorer of the two ears, but if the patient has found the hearing aid more effective for the poorer ear, or the tinnitus is worse in the better ear, operation may be done on the better ear. As a rule, if the hearing is essentially normal for one ear, operation is not done on the otosclerotic ear unless the tinnitus is especially severe in the otosclerotic ear, or the patient's occupation demands binaural hearing. In the 500 cases followed up for six months, or longer after operation, 351, or 70 per cent, have serviceable hearing. Of the 266 patients considered ideal for operation, 213, or 79 per cent, have serviceable hearing. Of 211 "borderline" patients, 137 or 66 per cent have serviceable hearing; of 23 patients considered non-suitable for operation on the basis of the cochlear nerve function, only 1, or 4 per cent, has serviceable hearing. Of patients followed up for one year or more, 66 per cent have serviceable hearing. Tinnitus was entirely relieved in 101, or 24 per cent of the 500 patients; and partially relieved in 299, or 54 per cent. The majority of these patients with complete or partial relief of tinnitus have serviceable hearing. The fenestra closed in the first six months in 39 or 8 per cent of the 500 cases; and between the sixth and the twelfth month in 12 cases or 4 per cent. In no case was there a closure of the fenestra after a year. In 16 cases a revision operation was done because of closure of the fenestra; 4, or 25 per cent of these patients, now have serviceable hearing for more than six months.

COMMENT

An excellent report of the results of the fenestration operation by an author whose experience is sufficiently large to make the report valuable. L.C.McH.

A Therapy of Proved Efficacy In Otomycosis

B. L. Bryant (*California Medicine*, 68:359, May 1938) describes the treatment found to be effective in the treatment of otomycosis in over 4,000 cases seen at a naval base hospital in the South Pacific. In these cases a secondary acute external otitis was present in addition to the underlying mycosis. Bacteriological examination of the exudate in the acute stage of the external otitis showed mixed flora with staphylococci predominating. This external otitis must be treated first. In cases with moderate inflammation and minimal swelling of the canal wall, the most effective treatment was found to be insertion of a cotton pledget covered with 5 per cent sulfathiazole ointment; this pledget was kept in place for twenty-four hours, when a fresh pledget was inserted. The ointment employed had a petrolatum base that could be thinned, if necessary, with liquid petrolatum. If the swelling of the ear canal was marked and furuncles were forming, or there was peri-auricular adenopathy, an x-ray treatment of 75 r was given, repeated, if necessary, in twenty-four to forty-eight hours. In cases in which the condition had been neglected and the adenopathy was marked and there was fever, the local treatment was supplemented by sulfathiazole given by mouth with the usual precautions. In rare cases where there was a sensitivity to the sulfa drugs, a Cresatin pledget was employed instead of the sulfathiazole pledget. When the acute external otitis had subsided, treatment of the underlying mycosis was begun. The characteristic findings in otomycosis are moist epithelial debris and gray or green deposits in the ear canal. In the treatment of otomycosis,

the exudate and debris must first be removed by irrigation, and the canal then completely dried; this must be done with care to avoid any injury to the canal wall. Patients were then instructed in the proper use of ear drops twice daily; the prescription for the ear drops was Hydrarg. Bichlor. (0.02) in alcohol (30.0). The patient was at first seen daily for cleansing of the ear canal, then the interval was lengthened to three days, five days, and one week. The ear drops were continued twice daily for at least two weeks after the ear canal was entirely free of exudate and debris, and then were used twice weekly for the following month. The importance of this last phase of treatment in preventing recurrences is emphasized. In the entire series of cases there was only one case of sensitivity to mercury—a mild skin reaction easily controlled. The mercurial ear drops were found to be almost universally successful in the types of mycotic infection found in the South Pacific. Mercury is not effective against *Aspergillus niger*, which is rare in the South Pacific, but is found more frequently in the United States. For this infection salicylic acid (0.75) in alcohol (30) is used for the ear drops, the general plan of treatment being the same as described.

COMMENT

It is interesting to note that after a very extensive experience with external otitis and a considerable amount of research in its therapy, the author has returned to time-honored prescriptions of mercury bichloride in alcohol or salicylic acid in alcohol. The reader must be careful to note that the author emphasizes meticulous cleansing of the external auditory meatus before one may expect any medicament to be of value.

L.C.McH.

RHINOLARYNGOLOGY

The Inhalation of Dust Penicillin

Louis Krasno and associates (*Annals of Internal Medicine*, 28:607, March 1948) describe a method of inhalation of dust penicillin, for which crystalline sodium penicillin, processed to number 100 mesh particles, is employed. The inhaler is de-

signed to deliver penicillin as a fine non-irritating dust to the respiratory tract; it is a simple device that can be used in the home or office as well as in the hospital. It consists of an oro-nasal face piece held on the face by an elastic head band. In the front of this mask there is a large exhalation

tion valve; the part of the mask around the chin contains a rubber sleeve with an inhalation valve which has a special detachable perforated metal chamber that contains the penicillin dust. The penicillin dust is inhaled through the inhalation valve, and is protected from the moisture of exhalation by the one-way inhalation valve which directs the inhaled air at a plane at right angles to the exhaled air. There is also a small hole on top of the mask just above the end of the nose; this allows air to be drawn in easily, avoiding any resistance on inspiration. This method of inhalation of penicillin dust was first used by 4 experimental subjects (including the authors) to determine if there were any irritating effects or other untoward effects of inhaling penicillin dust. When no ill effect could be demonstrated, the inhalation of penicillin dust was employed in 23 patients hospitalized for various types of respiratory disease, and in 39 ambulatory patients. In most of these cases the treatment was employed for upper respiratory infections, especially the common cold (acute rhinitis and/or acute nasopharyngitis), and in a few cases of chronic nasopharyngitis and chronic sinusitis. The hospital patients were given 100,000 units of penicillin dust by inhalation for twenty minutes three times a day. Most of the office patients were given only one treatment of 100,000 units, but occasionally more than one treatment was given. In the hospital patients, throat, nose and sputum cultures were examined before and after the penicillin dust therapy. It was found that there was a marked and rapid diminution of gram-positive bacteria in the upper respiratory tract under penicillin dust therapy; some of the gram-negative organisms were also diminished with the dosage used. In both the hospital and the office patients, the best results with the penicillin dust inhalation were obtained in the cases with acute upper respiratory tract infection, but there was also definite improvement in cases of chronic sinusitis and nasopharyngitis. In several of the hospital patients, determination of penicillin in the blood showed effective therapeutic levels three to three and a half hours after inhalation.

COMMENT

We refuse to make a bugaboo of an intramuscular needle and in our opinion 300,000 units of penicillin daily, intramuscularly, is more efficacious than penicillin used locally in the respiratory tract however elaborate the mechanism of applying it might be, L.C.McH.

Hemostasis in Tonsillectomy

G. M. A. Fortier (*Minnesota Medicine*, 31:493, May 1948) reports 350 tonsillectomies, 200 under general anesthesia and 150 under local anesthesia. There were 2 cases in which postoperative hemorrhage occurred in the local anesthesia group; in one case bleeding was due to slipping of a ligature; the blood vessel was easily religated again; in the other case no ligatures had been found necessary at the time of operation, but when moderate bleeding started twelve hours later ligation was done at the patient's bedside. In the group operated under general anesthesia, a hemorrhage occurred in a child six years of age forty-eight hours after operation and ceased spontaneously. There were 2 other cases in which hemorrhage occurred eight days postoperatively and was controlled by pressure for eight hours; the bleeding was from the lower pole where no ligatures had been applied at operation. In all other cases in the series of 350 cases there was no hemorrhage and the tonsillar bed was free of blood clots. In the prevention of postoperative hemorrhage in tonsillectomy, full exposure of the raw tonsil bed, and meticulous ligation of all bleeding vessels without including any excess tissue are essential. In the author's experience, usually not more than two or three vessels on each side require ligation. He has employed Rochester-Pean's curved forceps and the La Force "Y" tier for ligation of vessels in the tonsillar bed, with 00 catgut.

COMMENT

Sound surgical technique requires the ligation of bleeding vessels in either open or closed wounds. For twenty years it has been our routine to control bleeding points in tonsil fossae by suture ligatures with fine catgut. In our experience simple ligatures frequently come off the first time the patient gags. We doubt that an operator who finds this a too difficult or time consuming procedure should be removing tonsils, L.C.McH.

Influenzal Laryngitis

D. W. Brewer and J. H. Tom Rambo (*Annals of Otology, Rhinology and Laryngology*, 57:96, March 1948) report 6 cases of edematous laryngitis due to *H. influenzae*, type B, seen at the Massachusetts General Hospital between March and August 1947. Most of the cases of influenzal laryngitis reported in the literature occurred in children, but in the authors' series 4 patients were adults. This brings the total number of cases in adults to 6 thus far reported. One of the patients in the authors' series, an infant, nineteen months of age, was moribund when first seen; the onset of symptoms occurred ten hours before death. The throat culture and the blood culture were positive for *H. influenzae*, type B. Autopsy in this case showed marked swelling of the epiglottis and aryepiglottic folds; histological examination showed edema and cellular infiltration of the epiglottis that was submucosal in location; the inflammatory reaction in the larynx decreased from the epiglottis downwards. In the other 5 cases, the symptoms were sore throat, dysphagia and respiratory distress; there was a low-grade fever, but the patients "looked much sicker" than was indicated by the degree of fever and other clinical findings. The throat cultures were positive for *H. influenzae*, type B, and negative for Klebs-Loeffler bacilli. All patients showed marked inflammatory edema of the larynx, especially of the epiglottis. Lateral x-rays films showed marked swelling of the epiglottis in every case. The oldest patient, sixty-three years of age, required tracheotomy for relief of dyspnea. All the patients were treated with streptomycin; in one case (the first to be treated), sulfadiazine and penicillin were first used and the symptoms and epiglottic swelling began to subside, but recurred; under streptomycin therapy, there was rapid improvement. Of the 5 patients treated with streptomycin, 2, one child and one adult, made an uninterrupted recovery. In 2 in which an abscess of the epiglottis had developed, the symptoms cleared rapidly under streptomycin therapy, and the swelling was at first reduced rapidly, but complete resolution of the inflammatory edema of the epi-

glottis did not occur for nearly a month. In the case in which tracheotomy was done, the epiglottis appeared normal on the thirteenth day, but the use of the tracheotomy tube was continued until the thirtieth day, because of apparent abscess of the ventricular bands. The subsequent resolution of the lesion was slow, and biopsy of the false cords was done, because of the patient's age, but showed only chronic inflammation and no evidence of carcinoma. On the basis of the results in these cases, the authors consider that streptomycin is more specific against *H. influenzae*, type B, than any previously available therapeutic agent; penicillin may also be given in influenzal laryngitis to combat secondary coccal infections. The dosage of streptomycin employed was 0.5 to 1 gm. daily in children (according to age) and 2 gm. daily in adults, given in divided doses.

COMMENT

We have seen a number of cases of edematous laryngitis involving the upper portion of the larynx. In some of them tracheotomy has been necessary and nearly all have responded satisfactorily to sulfonamides and penicillin therapy. In those instances where response to this treatment is not definite or rapid, streptomycin should certainly be used. L.C.McH.

Operative Treatment of Ozena

A. Rethi (*Journal of Laryngology and Otology*, 62:139, March 1948) describes an operation for ozena employed for the last five years. This operation is now done in three stages. In the first stage a septum flap with its posterior base is excised; then the base of this flap is broken by a special instrument so that it becomes adjacent to the side of one meatus. The flap is fixed in position by a boric acid petrolatum gauze tampon introduced in the opposite meatus; the nostril of the meatus closed by the flap is protected by a gauze strip prepared like the tampon. The tampon is changed on the third postoperative day, then daily till the seventh day, when no tampon is used. On the eighth day the second stage of the operation is done; in this stage the anterior portion of the septum flap is inclined over to become adjacent to the lateral wall of the opposite (patent) meatus; a special retrac-

tor resembling the so-called French hook is employed for this purpose. A tampon is introduced and changed, as after the first stage, until the seventh day. The third stage operation can be done immediately after the second stage, or, in debilitated patients, after ten to fourteen days. The third stage consists in implantation of the duct of the parotid gland into the maxillary sinus on one side. This operation is done on one side only, so that there is not too abundant a flow of saliva into the nasal cavity during eating, but a continuous flow that keeps the nasal mucosa moist; the saliva passes from the operated side to the other side through the defect in the septum. During a five-year period, this operation has been

employed in 26 patients, although in the first cases implantation of Stensen's duct was not done. The results in the later cases have been better than in the earlier cases, but in all the dryness and crusting have been relieved. In the later cases, in which implantation of Stenson's duct was done, the mucosa appears entirely normal. Although the size of the air passage has been reduced by the operation there is no respiratory difficulty.

COMMENT

Only a rhinological surgeon can appreciate the technical difficulties of the operation described by the author. Ozena appears in this country much less frequently than 15 years ago but is a very difficult problem, L.C.McH.



Body Absorbs Only Minimum of Vitamin B₁

Apparently, vitamin B₁, taken in large doses in the hope that it will give extra pep and energy, isn't a potent builder-upper. It might be, only the body doesn't absorb enough of it, according to a Northwestern University scientist. Work by Dr. Theodore E. Friedmann of Northwestern University indicates that oral doses of more than 5 milligrams daily are largely wasted. Furthermore, in contrast to other vitamins, the continued administration of thiamin (vitamin B₁) occasionally leads to development of an allergic response.

American Academy of Pediatrics Committee for the Improvement of Child Health

Announcement was recently made by the American Academy of Pediatrics of receipt of a three-year grant of \$50,000 from the National Foundation for Infantile Paralysis. The fund will be used in support of the continuing program of the Academy's Committee for the Improvement of Child Health directed toward better and more evenly distributed medical care for children throughout the nation—state by state and county by county. The Committee for Improvement of Child Health, it was an-

nounced, will translate into terms of effective action the findings of a two-and-a-half year study of child health services just completed by the Academy. The Academy is a national organization of medical specialists in child care. Financed in part by previous grants from the Foundation and its county chapters, the study has determined just what services are available to children from the physicians, dentists, hospitals, and community health agencies in every part of the nation. Also included was an evaluation of pediatric education in all medical schools. Pilot state for the nationwide study was North Carolina, in which polio this summer reached epidemic proportions.

Importance of Early Diagnosis In Stomach Cancer

The time has come to abandon the old attitude of hopelessness toward cancer of the stomach and esophagus, declares Richard H. Sweet, M.D., visiting surgeon at the Massachusetts General Hospital, Boston, Mass. Writing in the July 31 issue of *The Journal of the American Medical Association*, Dr. Sweet says that "cancer of the stomach can be cured in an appreciable number of cases," provided that an early diagnosis is made and that the growth is of a reasonably favorable type.

Medical BOOK NEWS

Edited by
ANDREW M. BABEY, M.D.



SIR DOMINIC CORRIGAN
1802 ~ 1880

All books for review and communications concerning Book News should be addressed to the Editor of this department, 1313 Bedford Avenue, Brooklyn 16, N. Y. When books are sent to us with requests for review, selections for that purpose are promptly made.

Classical Quotations

● In conjunction with these may be reckoned the pulse, which is invariably full. When a patient affected by the disease is stripped, the arterial trunks of the head, neck, and superior extremities immediately catch the eye by their singular pulsation.

DOMINIC CORRIGAN

On Permanent Patency of the Mouth of the Aorta, or Inadequacy of the Aortic Valves.
Edinb. Med. & Surg. J. 1832, XXXVII, 225.

Postgraduate Psychotherapy

Psychotherapy in General Medicine. Report of an Experimental Postgraduate Course. By Geddes Smith. New York, Commonwealth Fund, [c. 1946]. 8vo. 38 pages. Paper, 25c.

The course was an experiment sponsored jointly by the Commonwealth Fund and the Division of Postgraduate Education of the University of Minnesota. Twenty-five physicians were chosen representing the practice of medicine under varying conditions in communities of assorted size. A two weeks' course in didactic and clinical psychiatry was undertaken. Many prominent psychiatrists with pertinent teaching experiences joined the teaching staff of the University in this experiment.

The report reveals what can be accomplished by the general doctor with psychosomatic orientation.

WILLIAM E. McCULLOUGH

Boyd's Surgical Pathology Revised

Surgical Pathology. By William Boyd, M.D. 6th Edition. Philadelphia, W. B. Saunders Co., [c. 1947]. 8vo. 858 pages, illustrated. Cloth, \$10.00.

This well known text still remains a classic in its field, being useful alike to both the medical student and the practicing surgeon. The new edition differs but little from the preceding, except in the inclusion of a chapter on the treatment of congenital heart disease and new material on lesions such as fibrositis of the back.

Dr. Boyd's style, while necessarily dogmatic in a one-volume text of this kind, is impressive largely because of his ability to provide perspective to the various surgical pathological processes and well reflects his outstanding ability as a teacher.

THEO. J. CURPHEY

Nerves

Mastering Your Nerves. How To Relax Through Action. By Larry Freeman & Edith M. Stern. New York, Harper & Bros., [c. 1946]. 12mo. 247 pages. Cloth, \$2.00.

Usually one hesitates to recommend a book of this kind which is intended to help those who are in need of psychologic guidance. However, the authors have presented their material in an enjoyable, common-sense manner and one need not worry that introspective individuals will be hurt by what they read. They have given us sound psychologic advice for living a well adjusted life, even though some of the platitudes give one the impression of over-simplification.

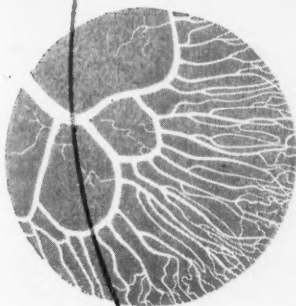
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Tuberculosis and Asthma

Tuberculosis y Asma Tuberculoso. By Dr. Román Alemany Vall. Barcelona, J. M. Massó, [c. 1946]. 8vo. 133 pages, illustrated. Paper, 30 Ptas. (Estudios Monográficos de Investigación Médica.)

The author, having been engaged for many years in the study of allergy, particularly in its respiratory manifestations, observed that there could be demonstrated quite often in asthmatic subjects, a tuberculous pulmonary lesion.

His conclusions are that tuberculous asthma is a common condition, that hypersensitivity to tuberculin is the origin of their asthmatic crises, that tuberculin reactions are much more pronounced in these patients than in "simple" tuberculous cases, that hypersensitivity to tuberculin causes typical allergic states such as eosinophilia, nasal polyposis, etc. before progressing to its usual fatal termination.

The treatise suffers from the enthusiasm of the true amateur who wrote it, and the specific theme of tuberculin as an allergen soon ramifies in the field of pulmonary tuberculosis in general.

DENNIS RYAN GILLEN

Internal Medicine

Internal Medicine in General Practice. By Robert Pratt McCombs, M.D. 2nd Edition. Philadelphia, W. B. Saunders Company, [c. 1947]. 8vo. 741 pages, illustrated. Cloth, \$8.00.

Here is a book on Internal Medicine in General Practice that contains only 740 pages. In this era that is a rare phenomenon. Another popular textbook devoted to the same subject contains 1730 pages.

One is curious to know how this discrepancy can be accounted for. A reading of the preface gives adequate explanation. "Controversial material," diseases "rare in the U. S.; condensed descriptions or omission of technical procedures;" by reducing all of the above to the minimum "it has been possible to encompass a broad field in a relatively small volume."

Not, however, without some sacrifice. For example: Typhoid Fever is discussed in a space of five pages here, while the larger book devotes thirteen pages to it. In Diseases of the Nervous System, we have the subject covered here in 52 pages, while in the larger work it takes 130 pages to present it. It must not, however,

be assumed that the quality differs in the same proportion. It accomplishes what it set out to do, to present a subject in as practical and succinct a manner as possible.

Therefore the reviewer suggests that the reverse of the usual procedure should be adopted here, namely that the larger volume should supply the text and the smaller the reference book. For the student, it offers an excellent medium for review.

S. R. BLATTEIS

Vitamins

Vitamine, Hormone, Fermente. Ein Buch für Ärzte, Biologen und Studierende. By Dr. Rudolf Abderhalden. 3rd Edition. Basel, Switzerland, Benno Schwabe & Co., [c. 1946]. 8vo. 250 pages, illustrated. Cloth, 14.50 fr.

This book provides a well-organized, up-to-date summary of all currently known vitamins, enzymes, and hormones. Intended primarily for doctors and biochemists, physiological action of these substances is stressed, and chemical properties are only briefly discussed. Included also are discussions of methods of assay and clinical applications, as well as a list of commercial preparations on the market, for each of the compounds. This book should be of invaluable help to the practicing physician, and at the same time, should provide a useful review for biologists and biochemists. It is regrettable that Dr. Abderhalden has failed to cite references to the original literature.

GEORGE KATZ

China in Wartime

A Surgeon in Wartime China. By Lyle Stephenson Powell, M.D. Lawrence, Kansas, University of Kansas Pr., [c. 1946]. 233 pages, illustrated. Cloth, \$2.50.

This book contains interesting descriptions of the social, political and military organizations of the Chinese, with whom Dr. Powell seems unusually sympathetic and with whom he seems to have maintained almost continuous friendly relations. Dr. Powell's experiences in the First World War and his subsequent wanderings, including a long trip deep into China, prepared him to an exceptional degree for the assignment which resulted in this book.

J. RAPHAEL